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PRESENT STATUS OF THE PROBLEM OF AMEBIASIS

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THE PROBLEM of amebiasis is becoming increasingly important to both the medical profession and the public as a result of the experience of physicians in the armed forces and with the return to the United States of men infected with the disease. Some writers have been unimpressed with the magnitude of the problem. In a discussion of problems of tropical diseases in returning military personnel, Meleney [1] stated that malaria and filariasis are of greatest concern. That these two infections constitute a serious problem in public health is widely recognized, but we submit that the number of troops exposed to filariasis in the Pacific was extremely small as compared with the number of those infected with amebiasis. Greene and Fisher [2] expressed the opinion that an increase in amebiasis is unlikely. On the other hand, there are writers who take the opposite point of view. Eusterman [3] stated:

> When Johnny comes marching home from tropical and subtropical countries, soldiers with amebiasis, . . . will be seen in increasing numbers by doctors more or less unfamiliar with tropical diseases. Even the larger military establishments are not above occasional error. Recently there came under my observation a young ensign who had been unsuccessfully treated for ulcerative colitis in a naval hospital over a period of 18 months. The frequent bloody discharges made such a diagnosis plausible. But the feces were found to be swarming with Endamoeba histolytica, and intensive treatment fortunately resulted in gradual but complete recovery.

Craig [4] wrote:

> At the present time, thousands of our troops are serving in regions where amebiasis is a common and often serious infection, and many of these men will

From the Department of Medicine, University of Wisconsin Medical School.

1. Meleney, H. E.: Problems of Treatment of Tropical Diseases in Returning Military Personnel, New York State J. Med. **44**:2105, 1944.

2. Greene, J. A., and Fisher, W. M.: Tropical Diseases in Texas in the Post War Era, Texas State J. Med. **40**:408, 1944.

3. Eusterman, G. B., in Dick, G. F.: Yearbook of General Medicine, Chicago, Year Book Publishers, Inc., 1945, p. 701.

4. Craig, C. F.: The Etiology, Diagnosis, and Treatment of Amebiasis, Baltimore, Williams & Wilkins Company, 1944.

return to the United States infected with Endamoeba histolytica, the cause of amebiasis. This will add to the already considerable percentage of infections with this parasite in this country, conservatively estimated at 10 per cent of the population, and will render the diagnosis and proper treatment of the infection of still greater importance from the standpoint of public health.

We subscribe to this view as a result of over three years' experience in the Pacific theater, where we were able to observe some filariasis, the usual amount of malaria and in addition a great many cases of amebiasis. There is sufficient reason for believing that most of the former infections were reported and brought under medical care, so that current estimates of their frequency are fairly complete. With amebiasis, on the contrary, only a small proportion of patients received medical attention, owing to the insidiousness of the infection and the universality of mild diarrhea and intestinal complaints sufficient to mask anything short of frank amebic dysentery. A considerable reservoir of unsuspected and unreported amebiasis has undoubtedly been brought back to the United States and civilian life; thus the magnitude of the public health problem created becomes apparent. It would therefore seem appropriate to call attention to the problem as it exists and to emphasize from personal experience certain principles found to be of value in the management of amebiasis.

EPIDEMIOLOGY OF AMEBIASIS

Amebiasis may be defined as infection with the protozoan Endamoeba histolytica, irrespective of the clinical manifestations (or lack of them) presented by the patient. The term includes asymptomatic invasion of the colon (asymptomatic cyst passer, or "carrier"), simple diarrhea, dysentery and hepatic and other extraintestinal infections. It should be emphasized that amebic dysentery and amebic abscess of the liver are not synonymous with amebiasis, for although they are a part of serious amebic infection they are, in the temperate portion of the United States at least, rarer manifestations of the disease. Were they to be made the criteria of diagnosis, then the vast majority of amebic infections would be entirely overlooked.

There are five common species of parasitic amebas in human beings, of which four are nonpathogenic and acquire importance only by virtue of the diagnostic confusion they create in laboratory identification of the fifth and highly pathogenic species, E. histolytica. Detailed information on morphology may be obtained from standard reference texts.[5]

The parasite has been found wherever surveys have been made in both hemispheres. Although the incidence and severity of infection

5. (*a*) Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 4, Philadelphia, Lea & Febiger, 1945. (*b*) Mackie, T. T.; Hunter, G. W., and Worth, C. B.: Manual of Tropical Medicine, ed. 1, Prepared Under Auspices of the Division of Medical Sciences of the National Research Council, Philadelphia, W. B. Saunders Company, 1945. (*c*) Craig.[4]

are greater in tropical climates and regions of poor sanitation, the disease occurs in a significant degree elsewhere. For example, in the northern United States, surveys reported from the same clinic over a number of years have shown rates varying from 4.5 per cent to 17.7 per cent, with the average around 12 per cent.[4] In warmer zones the incidence rates have been reported as high as 32 per cent in rural communities and 55 per cent in orphanages.[4] In all probability, the adjusted over-all incidence of infection in the United States as determined to date is in the vicinity of 10 per cent. Rates significantly higher than this have been reported in overseas theaters occupied by American troops.[4]

The life cycle of E. histolytica is simple in that, for practical considerations, only two stages exist. One is the motile, vegetative form, or trophozoite, and the other the nonmotile cyst. The former constitutes the invasive stage responsible for the lesions in the wall of the bowel and other organs and may be found in tissues so infected, on the surface of the intestine or within the lumen. Under the influence of dehydration and possibly other factors unfavorable for the existence of the motile form, encystment occurs in the lumen. With passage of cysts in the feces, transmission of infection is possible. Ingestion of cysts is followed by excystation in the intestine, with invasion in the ileocecal region, and the cycle is completed with the liberation there of new trophozoites.

It is now well established that the trophozoite is not an infectious form of the parasite. Transmission of the disease occurs only after ingestion of cysts, which may be disseminated through the mediums of water, food, flies and direct contact.[6] Indirect proof of the first may be had in the case of the outbreak in Chicago in 1933, in reduction of incidence of disease following installation of sanitary water systems and in certain instances during the recent campaigns in the Pacific, where polluted water afforded the main source of exposure. The medium of food assumes considerable importance in well sanitated region inasmuch as handlers of food may constitute the primary means of spread. This avenue is especially important in familial association, and it should be emphasized that in this situation the cyst-passing veteran will be encountered. Statistics on the incidence of infection in handlers of food are available.[4] Viable cysts have been found in flies caught in dwellings which house human passers of cysts,[7] illustrating the potentialities of this mode of transmission. Finally, direct contact has been

6. Faust, E. C.: Some Modern Conceptions of Amebiasis, Tr. & Stud. Coll. Physicians Philadelphia **11**:101, 1943.

7. Frye, W. W., and Meleney, H. E.: A Survey of Flies, Pigs, Fowls, Rats and Mice in a Rural Community for the Intestinal Protozoa of Man, J. Parasitol. **18**:118, 1931.

shown to be an important method of transmission of infection in orphanages,[8] as well as in hospitals for mental diseases and prisons.

PATHOLOGY OF AMEBIASIS

The pathogenicity of E. histolytica depends on two factors. The first is the ability of the parasite to secrete a potent cytolytic toxin, by means of which dissolution of the intact mucosa of the bowel may be affected. The second is its capacity for active ameboid movement. By a combination of these actions the parasite is capable of invasion of the lining of the entire large bowel, sigmoid, rectum, appendix and distant organs. The sites of predilection in the bowel (infection does occasionally occur in the terminal part of the ileum) are the cecal and rectosigmoid areas and, to a lesser degree, the two flexures, i. e., wherever stasis tends to be the greatest. Of these, the cecum must be recognized as the usual habitat of this organism. The earliest lesions are variable and are said to include pinpoint ulceration, shallow crater-like ulceration or shallow more extensive denudation of mucosa.[9] At this earliest stage the lesions are confined to the mucosa, and, depending on resistance of the host, it is likely that some spontaneous healing occurs. Should healing fail to occur, further penetration of the ulcers follows, with extension through the muscularis mucosa and expansion into the loose submucosa. By this process the classic flask-shaped ulcers result, with typical undermining of edges and sinus formation whenever the submucosal portions coalesce. Further penetration through the outer muscular layers into mesenteric venules and invasion of the portal vein provide the basis for amebic hepatitis or abscess and infection of other organs. Most typical of the gross appearance of the amebic bowel is the discrete nature of the ulcerations, with areas of normal mucosa between them. There is relatively little inflammatory reaction, so that scarring does not follow if the infection is treated early. It should be noted that amebic involvement of the cecum and appendix may masquerade as acute appendicitis with moderate frequency. In our experience, failure to observe this fact has been responsible for a great many unnecessary appendectomies.

THE "CARRIER" STATE

The "carrier" state in amebiasis refers to the asymptomatic passer of cysts. The latter term accurately describes this condition, while the

8. Ivanhoe, G. L.: Studies in the Transmission of Amebiasis in a Children's Home in New Orleans, Am. J. Trop. Med. **23**:401, 1943.

9. (*a*) James, W. M.: Human Amebiasis Due to Infection with Entamoeba Histolytica, Ann. Trop. Med. **22**:201, 1928. (*b*) Faust, E. C.: Amebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases, Am. J. Trop. Med. **21**:35, 1941.

expression "carrier" is unfortunately misleading. It connotes a situation in which the parasite is assumed to be living within the host as a harmless commensal, not at the expense of the host's tissues, in a manner analogous to a carrier of meningococcus of an avirulent strain, Eberthella typhosa or Corynebacterium diphtheriae. This erroneous belief is engendered by the large percentage (50 per cent) [4] of "carriers" who do not present symptoms of amebic infection. According to this spurious reasoning, since there are no symptoms there must be no pathologic change, and the belief is widespread that E. histolytica may live and multiply within the lumen of the bowel without producing lesions or that an avirulent strain exists. As a result the passer of cysts is lightly regarded and dismissed in a casual manner, when nothing is more unjustified if the facts of the condition be known. Hargreaves [10] has recently expressed this same point of view.

There is abundant evidence in the literature to discredit this belief. Such evidence strongly suggests that infection with the parasite always means invasion of the tissues, with the production of pathologic lesions, and that cysts from asymptomatic "carriers" are fully pathogenic. In 1913 Walker and Sellards,[11] working in Manila, fed to 20 human volunteers the cysts obtained from asymptomatic "carriers." Seventeen of the subjects became infected with parasites, in 4 of whom acute amebic dysentery developed later. Kessel [12] in 1928 showed that amebas from "carriers" are as pathogenic for experimental animals as those obtained from patients with acute dysentery. Spontaneous recovery sometimes occurred, periods of incubation were similar, pathologic lesions were identical and length of life of animals after feeding was the same when results from animals infected from the two sources were compared. Dobell [13] confirmed these conclusions in 1931. Faust,[14] as a result of studies on experimental amebiasis in dogs, stated that there is no detectable difference in susceptibility to human strains of an acute, chronic or carrier type. To date, no nonpathogenic avirulent strains of E. histolytica are known, so that the asymptomatic passer of cysts

10. Hargreaves, W. H.: The Treatment of Amebiasis with Special Reference to Chronic Amebic Dysentery, Quart. J. Med. **15**:1, 1946.

11. Walker, E. L., and Sellards, A. W.: Experimental Entamoebic Dysentery, Philippine J. Sc. (B) **8**:253, 1913.

12. Kessel, J. F.: Amoebiasis in Kittens Infected with Amoebae from Acute and "Carrier" Cases, and with the Tetranucleate Amoebae of the Monkey and of the Pig, Am. J. Hyg. **8**:311, 1928.

13. Dobell, C.: Researches on the Intestinal Protozoa of Monkeys and Man: IV. An Experimental Study of the Histolytica-Like Species of Entamoeba Living Naturally in Macaques, Parasitology **23**:1, 1931.

14. Faust, E. C.: Susceptibility, Resistance and Spontaneous Recovery in Dogs Experimentally Infected with Entamoeba Histolytica, Proc. Soc. Exper. Biol. & Med. **29**:659, 1932.

cannot be dismissed as harboring an avirulent strain. The evidence concerning the parasite's inability to live in the lumen without producing lesions is equally conclusive. Kessel [12] noted that pathologic lesions were present in the intestine in animals free of diarrhea or dysentery for as long as sixty-two days after inoculation. Hegner and others,[15] working with experimental amebiasis in monkeys, reported gross and microscopic lesions with trophozoites in situ in the tissues without the occurrence of diarrhea. Johnson [16] studied naturally occurring asymptomatic infections in 10 monkeys in Panama. In 9 no gross lesions were observed at autopsy, but microscopic section demonstrated that in 7 of the animals lesions were present containing the trophozoite. Studies on human pathologic material support these experimental observations. Musgrave [17] in 1910 reported 50 cases of persons dying of other diseases, without a history of diarrhea or dysentery or evidence of either in the hospital, who at autopsy had characteristic amebic lesions in the colon. Bartlett [18] in 1917 described 11 cases of patients, without a history of diarrhea before or after their admission to the hospital for wounds and other diseases, who showed extensive amebic ulceration of the intestine at autopsy. Faust [9b] in 1941 reported a study of amebiasis as revealed by autopsy of patients who died of accidents, in whom were found pinpoint ulcerations, shallow crater-like lesions and extensive extremely shallow denudation of mucosa with trophozoites in the lesions in some cases. The lesions noted represent the mildest type of damage to tissue reported in "carriers" and lend support to the belief that E. histolytica lives at the expense of the asymptomatic host. Craig [19] cited other cases of asymptomatic passers of cysts who had amebic ulcerations of the bowel at autopsy. Finally, it is a well known fact that in roughly one third of the cases amebic hepatitis develops in persons who have never experienced diarrhea or dysentery, a fact which strongly suggests that the "carrier" state is a pathologic condition warranting the same serious attention accorded other forms of the disease, since hepatitis is always secondary to invasive lesions of the wall of the bowel.

From the foregoing summary it may be concluded that the bowel of the asymptomatic passer of cysts is the site of pathologic change; that the pathologic change is qualitatively identical with that of amebic

15. Hegner, R.; Johnson, C. M., and Stabler, R. M.: Host-Parasite Relations in Experimental Amoebiasis in Monkeys in Panama, Am. J. Hyg. **15**:394, 1932.

16. Johnson, C. M.: Observations on Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys, Am. J. Trop. Med. **21**:49, 1941.

17. Musgrave, W. E.: Intestinal Amoebiasis Without Diarrhea. A Study of Fifty Fatal Cases, Philippine J. Sc. (B) **5**:229, 1910.

18. Bartlett, G.: Pathology of Dysentery in Mediterranean Expeditionary Force, 1915, Quart. J. Med. **10**:185, 1917.

19. Craig, C. F.: The Pathology of Amebiasis in Carriers, Am. J. Trop. Med. **12**:285, 1932.

diarrhea or dysentery and differs only quantitatively in tending to be of lesser degree, and that there is no foundation in studies either on animals or on human beings to regard the asymptomatic passer of cysts as a healthy "carrier." A clinical axiom might be drawn by stating that in amebiasis symptoms are not a reliable index of the extent of the pathologic lesions, for the latter may and usually do outstrip the former. We cannot emphasize too strongly our clinical impression that the "carrier" represents an active stage of the disease, often, if not regularly, completely free of symptoms and for this reason the most easily overlooked and neglected. It is the stage of the disease when the opportunity is greatest for prevention of serious and even fatal complications. It is the time when the best chance exists for complete eradication of the infection and for restoration of the patient to full health in the shortest possible time, with the lowest probability of troublesome sequelae. Surely no one would reserve definitive treatment in tuberculosis until cavitation developed. In amebiasis, as in tuberculosis, the time for full and complete therapy is as early in the course of the disease as it is possible to give it. This will be, in the vast majority of instances in the United States, in the stage represented by the asymptomatic passer of cysts.

THE MANAGEMENT OF THE PATIENT

An intelligent approach to the management of amebiasis can be made only after the fundamental facts pertaining to the epidemiology and pathology of the disease are understood. These have been reviewed, and special attention has been paid to the so-called carrier state. In discussing the management of the patient with amebiasis, we wish to stress several points: (1) the practical necessity of adopting a complete program of diagnostic procedures to be followed in every case, regardless of the stage of symptomatology; (2) the special problem of hepatitis; (3) the necessity for understanding the requisites of treatment, in view of what is already known about pathology, and the limitations of available drugs, and (4) the recognition of associated conditions, including bacillary dysentery and irritable bowel.

1. *Diagnostic Procedures.*—We believe it is wise to adopt a definite plan for the diagnostic investigation of patients with possible amebiasis, and we suggest that this plan should be followed consecutively in every case, irrespective of the particular phase of the symptomatology. In this way nothing of importance will be overlooked in the establishment of the correct etiologic, anatomic and functional diagnosis. A diagnostic program we have found useful is simple and can be applied anywhere. It includes the elicitation of a careful history, physical examination, proctoscopy, examinations of stools and, rarely, roentgenologic examinations.

History.—In approximately 50 per cent of patients there may be no history of intestinal disturbance, in which case cysts may have been discovered on a survey of handlers of food. In other instances a pattern of alternate constipation and diarrhea is important. Patients may recall having mushy semisolid stools three or four times daily for one or two days, followed by normally formed or constipated stools once a day or every other day for several weeks, or the patient may be first interviewed in the midst of a period of watery diarrhea amounting to six to eight stools a day without disturbance of sleep. Rarely, in the United States, will patients be seen with a present history of bloody stools every hour both night and day. The history of the bowel movements can thus vary widely from the cyst passer to the patient with frank dysentery. A parallel variation in intensity may be noted in the elicitation of a history of pain. The patient with the milder condition may well have no cramps. Accompanying a history of alternate constipation and diarrhea usually will be found a story of occasional colicky abdominal cramps referable to the cecum and large bowel, and with histories of severer disorder one finds increasing amounts of pain. Anorexia of mild or severe degree may be the sole or an accompanying symptom of importance. A history of melena is probably the least reliable point in most cases. It is always important to inquire for chills and fever, for in our experience their presence suggests a bacillary infection or, in the case of amebiasis, extension of infection to the liver. Uncomplicated intestinal amebiasis with or without diarrhea seldom accounts for a history of chills and fever. Finally, the possible occurrence of similar symptoms in the patient's family or associates, residence in an area of poor sanitation and a history of overseas service in the Mediterranean, Middle East or Pacific should make one suspicious of amebiasis.

Examination.—Examination may reveal nothing abnormal in the cases of asymptomatic infection, but in cases with alternate constipation and diarrhea it is common to find a boggy-feeling, gas-filled cecum that is sensitive to pressure. In more active infections there is usually tenderness over the course of the large bowel, especially at the flexures, which are sites of predilection. With active dysentery, the sigmoid will show tenderness in addition. The general condition of the patient is usually unaffected by the asymptomatic or mildly symptomatic disorders (hence the appellation "walking diarrhea"). Prostration, dehydration, tachycardia and fever are seen with frank dysentery. It is extremely important in every instance to determine the size of the liver, to note the presence or absence of tenderness if it is palpable and if it is not palpable to carry out gentle percussion over the liver anteriorly and posteriorly in a search for the point of tenderness. The mobility

or fixation of the right leaf of the diaphragm should always be ascertained in the examination. The significance of hepatic findings will be mentioned later. Cecal involvement by E. histolytica may masquerade as acute appendicitis, with pain in the right lower quadrant of the abdomen, tenderness and rigidity, slight elevation of temperature and some increase of the white blood cell count. This puzzling differential diagnosis was encountered with significant frequency in highly endemic areas during the war. Urinalysis and blood cell counts may be made as a part of the initial examination, but in our experience the results are within normal limits in uncomplicated intestinal amebiasis. Our experience substantiates the general belief that eosinophilia is not a manifestation of amebiasis, and its occurrence indicates the probable coexistence of helminthiasis.

Proctoscopy.—Proctoscopy should be a part of the initial study in every case of amebiasis, as it can provide invaluable information. Of special importance in this connection are color of the mucosa and the presence of bleeding points, pus, mucus, edematous areas and ulcerations. Often in asymptomatic patients the rectosigmoid will be normal in appearance, so that such an observation does not invalidate the etiologic diagnosis. Some patients, on the other hand, will be found to have scattered pinpoint ulcers when least expected, thus emphasizing the importance of proctoscopy. A typical early appearance indicative of the condition consists of scattered discrete ulcers, of whitish color, somewhat oval in shape, 1 to 2 mm. in length, situated with the long axis in the transverse axis of the bowel and surrounded by a bright red areola 2 to 3 mm. in width, with large areas of perfectly normal mucous membrane between and around them. We have observed mild conditions in which not more than one or two such tiny ulcers could be found after careful search. The location of the ulcers should be noted for future comparison. In severe diarrhea or dysentery the number of such ulcers increases, bleeding from them will be seen and the areas of uninvolved normal mucosa are less prominent. Observation of the foregoing picture is practically conclusive of amebic infection, but final diagnosis must await identification of the parasite. Following examination of the bowel, specimens are taken for laboratory examination. It is usually sufficient to collect several swabs of ulcerated areas, mucus or fecal material in a few cubic centimeters of warmed isotonic solution of sodium chloride, which can be taken to the laboratory directly without cooling. Ideally, the microscopic examination should be made at the proctoscopic table.

Examination of Stools.—Proctoscopic material is examined with exactly the same technic as that used for passed specimens, which may

be obtained if proctoscopic material fails to yield trophozoites or cysts. At least three daily naturally passed stools and one following administration of sodium sulfate or phosphate should be examined. A direct warm preparation in isotonic solution of sodium chloride should be searched for the motile trophozoites; a direct preparation in isotonic solution of sodium chloride or fecal preparation should be stained with a drop of D'Antoni's iodine (1.5 Gm. of powdered iodine crystals in 100 cc. of 1 per cent potassium iodide solution) and searched for cysts, and a third sample should be concentrated by the zinc sulfate method and then searched for cysts. These three technics should be employed on each sample taken to the laboratory. Details of laboratory technic are available in the manual of Mackie and others.[5b] In general, one expects to find cysts in a formed specimen and trophozoites or cysts in a diarrheic liquid specimen. Use of a bismuth preparation as a means of symptomatic treatment of diarrhea and the use of barium sulfate for roentgenologic study should be avoided at this point in the investigation, as they may prevent the demonstration of cysts for at least ten days after administration.

Roentgenologic Examination.—Roentgenologic examination is indicated in the diagnosis of hepatitis and is helpful in the study of irritable or scarred bowel. It is of no value in the early investigation of intestinal amebiasis. It is our belief that every case of amebiasis should be approached in some such orderly logical sequence in order to obtain the best results. For example, much time and expense will be saved by proctoscopy after the physical examination, for if proctoscopic material is found to contain the parasite, three or four days of repeated examination of stools may be eliminated entirely, and treatment may be started at once. If ulcers are found, one has an accurate base line by which to judge the effect of therapy with post-treatment proctoscopy, and if the mucosa is normal further proctoscopy is unnecessary.

2. *Hepatitis.*—Hepatitis poses a special problem, which can only be touched on here. It is important to remember that in at least 33 per cent of cases it develops in asymptomatic passers of cysts and in one series [20] it is reported a history of diarrhea or dysentery was obtained in only 32.7 per cent of cases of amebic abscess of the liver, i. e., in possibly two thirds of the cases the condition occurred in previously asymptomatic subjects. Thus the presence of diarrhea is helpful, but its absence means nothing. However, in the diagnosis of hepatitis the presence of E. histolytica in the stools is corroborative. Other signs and symptoms include spiking fever; chills; pain, which may be in the

20. Sodeman, W. A., and Lewis, B. O.: Amebic Hepatitis, Am. J. Trop. Med. **25**:35, 1945.

right upper quadrant of the abdomen, posteriorly over the liver or along the ridge of the trapezius muscle and related to respiration; nausea, anorexia and vomiting; tender liver on palpation or percussion; leukocytosis ranging from 12,000 to 30,000 cells, with increase in segmented neutrophils, and, finally, changes in the right leaf of the diaphragm. Roentgenologic examination is helpful in showing an elevation and fixation if roentgenograms are taken on both inspiration and expiration, and pleural effusion of the right lung can often be demonstrated. The absence of jaundice is helpful in distinguishing amebic from epidemic infectious hepatitis. In some instances diagnosis can be established only by observation of the response of the patient to a course of emetine hydrochloride. The treatment of amebic hepatitis is conveniently considered here. It consists of a full course of emetine hydrochloride, amounting to 10 grains (0.65 Gm.), with full courses of either carbarsone, chiniofon or diodoquin. Small abscesses probably respond to this therapy, while larger, well established abscesses require aspiration. The reader is referred to a recent paper by Ochsner [21] for a consideration of the surgical aspects of amebic abscess of the liver. It is important to remember that early diagnosis of amebic hepatitis permits cure by medical means alone. In addition to specific therapy, there are general supportive measures which are important in the management of extremely ill patients with amebic hepatitis. These include administration of sufficient plasma or albumin to maintain normal serum protein levels when anorexia and damage to the liver threaten the level of circulating protein and parenteral administration of dextrose in isotonic solution of sodium chloride to spare body protein and maintain a satisfactory balance of fluid and urinary output. The following cases are presented to illustrate two of the specific problems encountered in amebic hepatitis.

CASE 1.—An officer in the air corps, with a few months' tropical service, without history of diarrhea and dysentery, was well until one day before entry to the hospital, when he noted malaise, anorexia and feverishness. On the day of entry he complained of sudden onset of cough, dyspnea and pain in the right lower part of the chest anteriorly and laterally. Examination revealed an acutely ill dyspneic man with grunting respiration and splinting of the right lower part of the chest. The percussion note was resonant, breath sounds were transmitted and no rales or rub was heard over the right side of the chest. Considerable resistance was felt on palpation of the right upper quadrant of the abdomen, but it was impossible to feel the liver. Percussion over the right anterolateral costal margin was slightly painful. There was a leukocytosis of 12,000, with a normal differential count, while the rest of the laboratory work was noncontributory. A roentgenogram of the chest was normal. The first specimens of stool were

21. Ochsner, A., and DeBakey, M.: Surgical Amebiasis, Internat. Clin. **1**:68, 1942.

negative for E. histolytica. He had a septic course, with evening chilling and temperature of 102 to 104 F. and a fall in the morning to 99 and 100 F. He continued to complain of anorexia, dyspnea and pain in the right anterolateral costal margin. Pain developed along the ridge of the right trapezius muscle, the liver became definitely palpable in a few days and a second roentgenogram of the chest showed elevation of the right side of the diaphragm, without bulging. A specimen of the stool examined after a purge was positive for cysts of E. histolytica. Administration of emetine hydrochloride (1 grain [60 mg.] intramuscularly daily) was started, and this dose was continued for ten days. He was comfortable after the first two or three doses and became afebrile in four to five days. The tenderness on percussion was absent at the end of treatment. Chiniofon (0.5 Gm. three times a day) was given for ten days and followed by administration of carbarsone (0.25 Gm. twice daily) for ten days. He was ambulatory and feeling fine when transferred to another hospital for convalescence.

Comment.—This is an instance of how amebic hepatitis can provide a puzzling diagnostic problem when it appears in an apparently well person who has not had diarrhea or intestinal complaints previously. While the presenting symptoms suggested acute pleurisy, the absence of signs related to the chest and the presence of tenderness on percussion over the liver pointed to the correct diagnosis. The roentgenogram was helpful, the amebas in the stool were corroborative and the therapeutic response to emetine hydrochloride clinched the diagnosis.

Case 2.—In a soldier who had served under extremely poor conditions in the southern Philippines for many months, watery diarrhea developed about two weeks before entry. He was given nonspecific therapy on sick call and became constipated. He took a purgative for this, following which severe diarrhea, cramps and tenesmus ensued. He was admitted to a hospital, where E. histolytica was reported in the stools and treatment begun with diodoquin. This failed to control the diarrhea. Emetine hydrochloride (1 grain [60 mg.] intramuscularly daily) was given for three days, with lessening of diarrhea. However, chills, temperature of 103 F. and pain in the right upper quadrant developed. A diagnosis of amebic abscess of the liver was considered, but administration of emetine hydrochloride was discontinued and the patient transferred to another hospital. On entry, he was in severe pain, acutely ill and appeared dehydrated and debilitated. The temperature was 103 F. The most important finding was an exquisitely tender liver enlarged downward 15 cm., with accompanying painful hyperesthesia of the overlying skin. There was a leukocytosis of 25,000, and the roentgenogram of the chest showed elevation and fixation of the right side of the diaphragm. Emetine hydrochloride therapy (60 mg. daily) was resumed, and it was continued for seven days, making a total of 10 grains (0.6 Gm.) received in the two hospitals. During this week he was unable to eat or retain liquids, mild icterus developed, hypoproteinemia with edema of the ankles appeared and mild circulatory collapse was evident. He was given two transfusions of whole blood and repeated injections of plasma, dextrose and isotonic solution of sodium chloride, and he was able to retain fluids and food by mouth. By the end of the course of emetine hydrochloride the pain and tenderness of the liver had disappeared completely, but the fever continued irregularly, the temperature occasionally reaching 103 F. in the evening and at other times remaining around 99 F. Cough and sputum and rales over the lower fields of both lungs developed. A roentgenogram of the chest revealed four round discrete areas of increased density suggestive of early abscess formation, two in each lower lobe. There were no signs of infiltra-

tion above the right side of the diaphragm to suggest direct spread from a subdiaphragmatic source. It seemed unlikely that he had pulmonary abscess from amebiasis, since he had just completed one course of emetine hydrochloride. Sulfadiazine therapy was given for one week, without effect. The danger of toxicity involved being recognized, it was decided to give another course of emetine hydrochloride to see whether any effect could be obtained on the pulmonary process. Administration of another 7 grains (0.42 Gm.), given in doses of 60 mg. daily, had no effect. Administration of penicillin was resorted to, and in four weeks the roentgenogram of the chest was normal, the sputum and cough ceased, the temperature became normal and decided subjective improvement was made. In the meantime, a ten day course of chiniofon and carbarsone had been given and the stools became negative for E. histolytica. The patient was transferred to the United States because of prolonged hospitalization.

Comment.—In contrast to the first case, the diagnosis presented no difficulty, as the hepatitis developed in the presence of a recognized amebic diarrhea. The case provided an almost overwhelming therapeutic problem because of the degree of failure of the liver and inanition accompanying the amebic hepatitis. Administration of emetine hydrochloride plus supplementary protein, dextrose and fluids seemed to rectify the situation. The cause of the pulmonary complication was unexplained, although the therapeutic response is against an amebic origin (resistant to 17 grains [1.10 Gm.] of emetine hydrochloride) and favors a bacterial origin.

3. *Requisites of Treatment.*—It is the aim of specific therapy to eradicate all parasites from the host. To do this, one must take into account pathologic changes of the disease and limitations of the available drugs. From the section on the "carrier" state, it is clear that invasion of the tissue by the amebas must be expected in every case of amebiasis. Perhaps this concept is not capable of proof in every instance; yet when the clinician considers the individual case before him there is no way for him to say that this is the one in which invasion of the tissues has not occurred. Hence, the logical course is to expect invasion in all cases and plan therapy with this in mind. It is now possible to divide the infecting parasites into two groups according to location. The first comprises the trophozoites within the tissues, whether the mucosa, submucosa or muscularis of the colon, the mesenteric venules or liver or other areas. The second comprises both trophozoites and cysts outside of the tissues, i. e., in the lumen admixed with fecal material or on the surface of the bowel. Rational therapy must be planned to reach and destroy parasites in both groups. At this point it is necessary to take into account the limitations of the available drugs. Emetine hydrochloride given parenterally acts solely on trophozoites within the tissues, i. e., the first group, and there it is extremely efficient, as witnessed by the dramatic response of hepatitis or severe dysenteric symptoms to its administration. It leaves relatively untouched, however, the trophozoites and cysts outside the tissues, i. e., the second group, in the lumen or

on the surface of the bowel. For this reason it will not eradicate amebiasis, for unharmed trophozoites will continue to invade, and cysts will undergo excystation, and after a period of remission symptoms will return. Emetine hydrochloride is therefore of proved efficacy against the amebas only after they have invaded the tissues. The enteric drugs, such as chiniofon, diodoquin, vioform and carbarsone, act on trophozoites and cysts of the second group, within the lumen of the bowel. There they are efficient, just as emetine hydrochloride is within its sphere. What effect, if any, they may have on trophozoites which have already invaded the tissues is an open question. There is a common assumption that these drugs do reach them, but it is an assumption and not based on fact. We do not know of any instances in which amebic hepatitis has responded to chiniofon or carbarsone. Nor do we know of any studies which demonstrate that any of these drugs are absorbed in therapeutic concentrations. Chen [22] demonstrated that arsenic could be recovered from the urine in small amounts after ingestion of carbarsone (a total of 8 per cent of administered arsenic after fifty-two hours in 1 subject and 13 per cent after forty-two hours in the other), but it is unjustifiable to assume that excretion of elemental arsenic proves the absorption of carbarsone. It is true that David [23] and his co-workers showed that an increase in blood iodine occurred after administration of vioform and diodoquin, but this does not prove that the iodine measured was still bound in the compounds fed, an extremely important point. We maintain that it remains to be shown that they are effective on trophozoites actually within the tissues. It may be seen that emetine hydrochloride and the enteric drugs are complementary, one having its action on parasites within the tissues and the other on parasites within the lumen of the bowel. Knowing this and taking into account the invasion of the tissues and resultant separation of the organisms into two groups, it is possible to recommend therapy logically designed to eradicate all parasites from the host.

Complete amebicidal therapy ought to include use of both emetine hydrochloride and one or more enteric drugs if the maximum degree of effective protection of the patient is to be attained. This statement we believe to be equally true for all forms of amebiasis, regardless of the phase of symptomatology. It is realized that this represents a departure from opinion expressed in the textbooks,[24] in which one finds the

22. Chen, M.; Anderson, H. N., and Leake, C. D.: Rate of Urinary Arsenic Excretion After Giving Acetarsone and Carbarsone by Mouth, Proc. Soc. Exper. Biol. & Med. **28**:145, 1930.

23. David, N. A.; Phatak, N. M., and Zener, F. B.: Iodochlorhydroxyquinoline and Diiodohydroxyquinoline: Animal Toxicity and Absorption in Man, Am. J. Trop. Med. **24**:29, 1944.

24. Craig.[4] Craig and Faust.[5a]

recommendation to use an enteric drug alone in the treatment of the "carrier" and of mild amebic diarrhea, reserving emetine hydrochloride for control of dysenteric symptoms and hepatitis. Nevertheless, it is believed that a critical appraisal of the pathologic changes of the infection and the characteristics of the drugs supports our view.

For the treatment of the asymptomatic passer of cysts and the patient with mild diarrhea it is suggested that emetine hydrochloride be given in total amounts of 5 or 6 grains (0.3 or 0.36 Gm.) in divided doses of 1 grain (0.060 Gm.) daily. This should be sufficient to destroy the trophozoites that have invaded the intestinal wall and that must be reached via the blood stream. For the treatment of more massive invasions, such as acute dysentery and hepatitis, larger doses of emetine hydrochloride up to the full 10 grains (0.6 Gm.), are indicated. These total dosages are for persons weighing about 150 pounds (68 Kg.). While heavier persons should not ordinarily receive more, it is advisable in the case of much lighter subjects to reduce the total dosage on an approximate basis of 10 mg. per kilogram. The amount corresponding to 10 grains (0.64 Gm.) is then given over ten days' time, and that corresponding to 5 grains (0.32 Gm.) is given over five days. Under extreme necessity, a short course of emetine hydrochloride may be repeated after a rest period of ten days, provided strict precautions are observed and administration of the drug is discontinued at the earliest sign of toxicity. Certain care is necessary in the use of emetine hydrochloride. The patient must be asked to stay in bed from the third day of therapy to the second day after its completion. Bathroom privileges should not be allowed. It is wiser to write the order for one day's dose at a time, in order to avoid the chance for medication to be inadvertently continued as a part of routine nursing orders. The pulse rate and blood pressure should be measured daily, and electrocardiograms, if available, usually give additional valuable information. The patient should be seen daily while receiving emetine hydrochloride and examined by the physician, care being taken to note any irregularity of pulse, and inquiry should be made as to any soreness of the muscles, especially in the scapular regions. Use of the drug should be stopped if reasonable belief exists that appearance of extrasystoles or tenderness of the muscles is due to the therapy. (The toxic action of emetine hydrochloride is chiefly on cardiac and striated muscle. It is excreted extremely slowly, so that six to eight weeks are probably necessary for total elimination.) The use of the enteric drugs is uniform regardless of the phase of the infection. They are given until repeated examination of the stools fails to show the presence of trophozoites or cysts. Chiniofon is used in dosages of 0.5 to 0.75 Gm. three times a day, given after meals, for ten days. It is stated that one course will eliminate 90 per cent of infections as deter-

mined by examination of the stool. A second course will almost always be sufficient. Side effects include a sensation of rectal burning or itching and mild to violent diarrhea. The latter is believed to be helpful in sweeping parasites out of the bowel but can be regulated by adjusting the dosage or by the use of camphorated tincture of opium so that one or two loose stools a day result. Diodoquin has been recommended by D'Antoni [25] in doses of 0.6 Gm. three times a day for twenty days. He reported a 95 per cent cure with one course of treatment with this drug. It is believed to be as safe as chiniofon and less apt to produce uncomfortable side reactions. Carbarsone, the best of the arsenical preparations, is used in dosages of 0.25 Gm. twice a day, after meals, for ten days. One course will eliminate from 85 to 95 per cent of infection. Side effects are occasional headache and light headedness. It should not be used in the presence of known sensitivity to arsenic (dermatitis and optic atrophy). We have not encountered any intolerance to it in cases of epidemic infectious hepatitis, although the statement is made that it should not be given in the presence of hepatic disease. The usual plan of treatment is to start the patient on a course of carbarsone and follow with one of chiniofon, or vice versa, as by this method no rest period need intervene between courses. An alternate method is to give one twenty day course of diodoquin. The first course is given concurrently with the emetine hydrochloride, as time is saved and no harmful effects have been observed. After use of emetine hydrochloride is discontinued the patient may be treated while ambulatory if symptoms warrant it. Following completion of enteric treatment three daily examinations of the stools are done. If they are positive for parasites, another course of enteric treatment is given, but if sterile, it is desirable to recheck on approximately the fifteenth, sixteenth and seventeenth days after completion of treatment before the patient is dismissed as cured. An adequate follow-up consists of a monthly check of the stools for three months and then every three months for nine months, or a total of one year. It is desirable to have the periodic examination of the stools made of a purge specimen, as this will give the highest percentage of specimens positive for parasites with the least expenditure of time and expense. (It detects at least 75 per cent of cases which might be ultimately discovered, as high a percentage as can be revealed by examining six consecutive normally passed stools.[26])

A divergence of opinion still exists relative to the best drug to use in the treatment of amebiasis. British authorities have usually favored

25. D'Antoni, J.: Further Observations on Amebic and Bacillary Colitis in the New Orleans Area, Am. J. Trop. Med. **23**:237, 1943.

26. Andrews, J.: The Diagnosis of Intestinal Protozoa from Purged and Normally Passed Stools, J. Parasitol. **20**:253, 1934.

the use of emetine and bismuth iodide given orally in doses of 3 grains (0.18 Gm.) as a loose powder in gelatin capsules each night for twelve consecutive days. Hargreaves has written an excellent summary of this point of view.[10] American physicians in general have employed emetine hydrochloride given by intramuscular injection in doses of 1 grain (0.060 Gm.) for eight to ten consecutive days. Since no directly comparative study is available to settle the relative efficacy of these two preparations, it is not possible to resolve this question. The latter method has the possible advantage of insuring absorption of the entire dose and delivery of that amount to the tissues invaded by the organism. On the other hand, its efficacy in curing amebic dysentery has been estimated not to exceed 25 per cent, but when used in conjunction with chiniofon to attack the organisms in the intestinal lumen this therapeutic efficiency is greatly enhanced and, in the opinion of many, exceeds the effectiveness of emetine and bismuth iodide.[27]

Hargreaves [10] has made a valuable contribution to the treatment of chronic intestinal amebiasis through the use of the sulfonamide drugs and penicillin as preparatory medication to the use of the amebicidal drugs, in order to combat the secondary bacterial invaders which often complicate enteric infections, most of which are sensitive to one or the other of these preparations. The results he reported from the use of this plan of therapy are brilliant and justify unqualified recommendation of these accessory drugs, especially in chronic conditions which are likely to be unusually resistant to treatment.

Nonspecific treatment in intestinal amebiasis will probably be necessary in cases of dysentery or severe diarrhea. Rest in bed and a low roughage diet are the two most important considerations. For severe cramps, the use of 0.032 Gm. of phenobarbital and 0.032 Gm. of codeine every four hours as needed is valuable. If dehydration is a problem, it is best corrected by use of isotonic solution of sodium chloride intravenously.

4. *Associated Conditions.*—Recognition of such conditions is frequently of importance in the care of a patient with amebiasis. Two of these will be discussed, the first of which is bacillary dysentery. This is apt to cause confusion should the patient present himself while having frequent loose stools. The distinction may usually be made on proctoscopic examination when in the case of bacillary dysentery the mucosa is uniformly involved. There are no normal areas spared as in amebiasis. The bacillary process is one of more or less intense erythema, edema, possibly many small bleeding abrasions and much mucopurulent exudate on the surface. Microscopic examination of

27. Faust, E. C.: Personal communication to the authors, 1946.

the exudate in suspensions of isotonic solution of sodium chloride reveals pus cells in large numbers, whereas in amebiasis one sees only an occasional monocyte or a few red cells. A culture planted at the time of proctoscopy, if the appearance suggests bacillary infection, is a third means of differentiating the two conditions. If these diagnostic criteria are present and sulfonamide therapy is given, the response will help to decide the cause of the dysentery. Approximately 10 per cent of the patients with amebiasis in our experience have had associated bacillary dysentery. It must be remembered that the asymptomatic passer of cysts may have a superimposed Shigella infection which brings him to the physician or that, following such an infection, a previously unsuspected amebiasis may become clinically active. The latter point should be recalled before failure of treatment is admitted or before a diagnosis of chronic bacillary dysentery is made. The second condition frequently associated with amebiasis, or perhaps oftener following it, is the irritable bowel. The patients with this syndrome do not have cysts in their stools, and so far as can be determined they are cured of their infection. They complain of crampy abdominal pain, usually not well localized, generally coming after meals and nearly always made worse by foods of high bulk, e.g., string beans, cabbage, whole tomatoes and dry cereals. They will also note some irregularity of bowel habits, varying from looseness to constipation. Frequently they resort to laxatives, which adds to the difficulty. On examination they may have borborygmi, sometimes tenderness over the colon and signs of an unstable autonomic nervous system. Proctoscopy is noncontributory. Barium enema usually shows an increased motility of the colon, with spasm and decreased emptying time, conditions which may be produced occasionally by the administration of castor oil in preparation for roentgenologic examination, which is a point to consider in ordering roentgenograms of such patients or in their interpretation. This syndrome is especially liable to follow a long-standing amebic infection of the bowel and is not common in patients treated early. The condition is not per se a basis for diagnosis of psychoneurosis. It may persist for several months. The treatment of most value is the insistence on a low roughage diet, the strict avoidance of tobacco and all laxatives, the use of liquid petrolatum at bedtime if needed for obstipation and use of belladonna or occasionally codeine or phenobarbital in doses of 0.032 Gm. each for cramps.

SUMMARY

Attention is directed to the problem of amebiasis. From personal experience emphasis is laid on certain principles found to be of practical value in the management of this condition. The salient facts concerning the epidemiology and pathology of this infection are briefly

reviewed, and the epidemiologic importance of cyst-passing veterans is emphasized. The so-called carrier state is discussed, and evidence is presented to show that there is no such condition as a healthy "carrier" of amebiasis. Rather, the asymptomatic passer of cysts must be considered to be in an active stage of the disease, a fact of utmost importance to the health of the person and of the public. The management of patients embraces at least four considerations: 1. A diagnostic program is outlined in detail. 2. The special problem of hepatitis is illustrated with histories of 2 cases. 3. The question of specific therapy is discussed and a rational basis presented for the use of both emetine hydrochloride and enteric drugs in every case of amebiasis, regardless of symptomatology. 4. The differential diagnosis and treatment of the two most commonly associated conditions, bacillary dysentery and irritable bowel, are discussed.

HEMOLYTIC STREPTOCOCCIC SORE THROAT

The Course of the Acute Disease

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THE INITIAL phase of acute sore throat caused by group A hemolytic streptococci in young men has been previously described elsewhere.[1] Special attention was paid to the symptoms, signs and results of clinicopathologic and bacteriologic studies. Exudative tonsillitis was a frequent manifestation of streptococcic respiratory disease, but this sign was absent in many cases. Edema of the pharyngeal tissues and tender adenitis in the anterior cervical region were emphasized as abnormalities which were of value in the recognition of infection by hemolytic streptococci. Atypical cases were described, in which no definite evidence of streptococcic infection could be obtained by clinical study in the absence of serial antibody determinations. A cutaneous rash was associated with streptococcic sore throat in only a few cases.

This paper has been prepared for the purpose of recounting the subsequent events which occurred in this group of patients during the initial phase of the disease and the suppurative complications that followed. Certain bacteriologic and clinicopathologic information that was obtained will also be described. The nonsuppurative disorders that were often initiated by infection with hemolytic streptococci and the

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The laboratories of the Department of Medicine, Stanford University School of Medicine, were made available to the Commission for certain purposes.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

The cooperation and assistance of Colonel T. E. Harwood Jr., Major James Blanton and Captain Howard Coggeshall are gratefully acknowledged. The study was made possible by the devoted efforts of Elizabeth Randall, Viola Ferris, Loraine Kerr and Helen Rantz, who were responsible for the technical and secretarial work.

1. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract: A Comparative Clinical Study, Arch. Int. Med. **78**:369 (Oct.) 1946.

immunologic phenomena that were observed will be considered in other papers.[2]

METHODS

The methods used and the nature of the group studied have been described.[1] Patients admitted to a large station hospital and believed, on clinical and bacteriologic grounds, to be suffering from acute respiratory infection caused by group A hemolytic streptococci were accepted for detailed consideration. Frequent clinical examinations were carried out over a period of ten days in the hospital, and the men were seen again in follow-up at the end of the third week of illness. Many were observed more frequently and for longer periods. The throat and nose were repeatedly swabbed while the patient was hospitalized and again on follow-up. Swabs were streaked on the surface of mule blood agar plates and the isolated hemolytic streptococci classified into groups and types by the precipitin technics of Lancefield.[3] Total leukocyte counts were done on approximately the second and tenth days of illness and erythrocyte sedimentation rates (Westergren) on the second, tenth and twenty-first days. Serial determinations of the antistreptolysin and antifibrinolysin titers of the serum or plasma were often carried out.[4]

Four hundred and ten men were originally included in the group of cases believed to be examples of infection by group A hemolytic streptococci. Serial antibody determinations were made in 342, and a significant response[5] was discovered in 300. The latter may be regarded as proved cases of hemolytic streptococcic disease. This report will be based on an analysis of the records of these 342 cases and particularly of 299 in which detailed clinical and laboratory data were available and in which a complete follow-up examination was made.

SEROLOGIC TYPES

A total of twenty-six different serologic types of group A hemolytic streptococci were isolated from patients in the study group, of which only six (types 3, 17, 19, 30, 36 and 46) were each responsible for 15 or more cases. The natural history of the disease process caused by these six types has been analyzed, although the number of persons in each group is small, since the detailed information obtained during this study has not been previously available and because the organisms of the six types differed in regard to certain biologic characteristics.

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2. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: (*a*) Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945; (*b*) Hemolytic Streptococcus Sore Throat: The Poststreptococcic State, Arch. Int. Med., to be published; (*c*) Hemolytic Streptococcus Sore Throat: Immunologic Observations, to be published.

3. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

4. (*a*) Rantz, L. A., and Randall, E.: A Modification of the Technique for Determination of the Antistreptolysin Titer, Proc. Soc. Exper. Biol. & Med. **59**:22, 1945. (*b*) Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

5. A "significant response" was defined elsewhere.[1]

Infection by types 17 (28 cases), 19 (42 cases) and 30 (20 cases) was similar in that a moderate antistreptolysin response was regularly stimulated and that an increase in antifibrinolysin occurred in approximately half of all cases. A scarlatiniform rash appeared in nearly all persons with a positive reaction to the Dick test, and reactivity of the skin to Dick toxin was lost during convalescence. Infections by type 3 (33 cases) were followed by a much greater increment of antistreptolysin and a much less frequent antifibrinolysin response than those just described. Furthermore, a cutaneous rash was observed in only 1 case, but reaction to the Dick test of the skin regularly became negative during convalescence.

Infection by types 36 (58 cases) and 46 (15 cases) was never associated with a rash or reversal of the Dick reaction. The antistreptolysin response was comparable in both groups, but disease caused by type 46 was almost always followed by a sharp increase in antifibrinolysin whereas that caused by type 36 usually was not. The full evidence on which these statements are based will be presented elsewhere.[2e]

THERAPY

One of the following therapeutic regimens was instituted in each case on the first or second day in the hospital. Their effect on the course of the disease has been presented [6] but will be briefly reevaluated here.

Symptomatic.—Patients receiving only symptomatic therapy gargled frequently with hot solution of sodium chloride and received codeine as necessary for the relief of pain and discomfort. No salicylates or antibacterial agents were administered.

Sulfadiazine.—Four grams of sulfadiazine was administered by mouth as an initial dose, followed by 1 Gm. every four hours day and night. The average total dose for the group was 39 Gm. and the duration of therapy six and a half days.

Salicylates.—Ten grams of sodium salicylate was administered by mouth each day for approximately one week.

Penicillin Followed by Sulfadiazine.—Two hundred thousand units of penicillin was administered intramuscularly in eighteen to twenty-four hours, the individual injections being given at intervals of four hours. A standard oral course of sulfadiazine was begun with the last dose of penicillin, an average of 33 Gm. being given in five and four-fifths days.

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6. Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: An Evaluation in Tonsillitis, Nasopharyngitis, and Scarlet Fever, Arch. Int. Med. **77**:260 (March) 1946.

Penicillin (Short Course).—Two hundred thousand to 400,000 units of penicillin was administered intramuscularly in divided doses at four hour intervals in from thirty-two to sixty-four hours.

Penicillin (Long Course).—Five hundred thousand or 1,000,000 units of penicillin was administered intramuscularly in divided doses at four hour intervals in eighty hours.

The hemolytic streptococci isolated from many patients who had received a sulfonamide compound or penicillin were tested to determine the sensitivity of the organisms to these agents.[7] Thirty-two strains, recovered from men in whom sulfadiazine had been utilized alone, were studied. Five were resistant to 1 mg. and twelve to 5 mg. of sulfadiazine per cubic centimeter. Twenty-six strains obtained from as many patients in the group receiving penicillin followed by sulfadiazine were similarly tested. Eight grew in the presence of 1 mg. and eight in 5 mg. per cubic centimeter of sulfadiazine. Strains were available in 75 per cent of the cases in which penicillin had been administered. All were inhibited by 0.05 unit per cubic centimeter or less of this chemical.

For the purpose of certain comparisons, the number of cases in each category became too few if the treatment groups were subdivided on the basis of the sensitivity of the etiologic agents to sulfonamide drugs. All cases in which a sulfonamide compound was administered therapeutically, either alone or preceded by penicillin, were tabulated together. One group (33 cases) was established in which the isolated hemolytic streptococcus grew in 1 or 5 mg. of sulfadiazine per cubic centimeter, and another (25 cases) was established in which the organisms were completely inhibited by the smaller amount of the drug.

CLINICAL OBSERVATIONS

The clinical manifestations of the initial phase of acute sore throat caused by group A hemolytic streptococci have been presented elsewhere [1] and will not be recapitulated.

The infectious process caused by each of the six previously described types of hemolytic streptococci has been compared with regard to the frequency of occurrence and the severity of sore throat, headache, generalized aching, coryza, chills, hoarseness, pharyngeal exudate, edema, redness, tender adenitis of the anterior cervical region and cutaneous rash. A scarlatiniform rash occurred only in association with infection by types 3, 17, 19 or 30. No other significant [8] differences were dis-

7. Wilson, A. T.: Method for Testing in Vitro Resistance of Group A Hemolytic Streptococci to Sulfonamides, Proc. Soc. Exper. Biol. & Med. **58**:130, 1945.

8. The various percentages were compared throughout by a simplified method devised by Professor Holbrook Working, of Stanford University, for the determination of the approximate standard deviations of fractions. Differences greater than twice the standard deviation of the mean were required as an index of significance.

covered in the initial clinical manifestations of the disease caused by these serologic types of hemolytic streptococci.

The course of the disease has not been previously described and will now be considered.

Maximum Temperature.—Fever was noted during the period of hospitalization of nearly all these men, since afebrile patients were not admitted to the section of the hospital for patients with respiratory disease. The relationship of the maximum recorded temperature to a number of features of hemolytic streptococcic sore throat is portrayed in table 1. A rise in temperature to 102 F. or more occurred in 63.3 per cent and to 103 F. or more in 40.0 per cent of 300 proved cases. Low grade fever was uncommon, only 6.6 per cent of these patients having constantly maintained a temperature of less than 100 F. The presence of an antibody response, tonsils or cutaneous rash had no significant effect on the height of the temperature, nor did the amount of exudate present in the throat. Absence of tender cervical adenitis was associated with significantly less febrile illness.

Infection by types 3, 17, 19, 30, 36 and 46 resulted in a comparable range of maximum temperatures. The data on which this statement is based have been omitted.

Duration of Fever.—The duration of fever will be treated in a similar manner. The essential data are included in table 2. Seventy-one per cent of the patients with proved streptococcic infection were afebrile within three days and 85.7 per cent within four days. The presence or absence of tonsils or of an antibody response did not alter these values. Patients in whom a cutaneous rash was observed were febrile for a much longer time, an elevated temperature having been noted for five or more days in 48.1 per cent of this group. Neither the severity of tender cervical adenitis nor the amount of exudate in the throat could be correlated with the length of the febrile illness.

The type of Streptococcus affected the duration of fever, since infection by types 17, 19 or 30 was accompanied with a more prolonged (five or more days) febrile course than was that caused by types 3, 36 and 46. Analysis of the data reveals that this was the result of the inclusion of many patients with rash in the first three groups.

The last section of table 2 reveals that the duration of fever was longer in patients treated with various antibacterial agents than in the group as a whole. The relatively higher initial leukocyte counts (table 6) and the large number of instances of cutaneous rash (18 cases) in treated patients indicate that these were more severely ill and explains in part the prolonged febrile illness in these persons. In 5 cases, a relapse, following inadequate penicillin therapy, was the cause of prolonged initial fever. Cases will be mentioned later in which this phenomenon occurred, but they are not considered here because the tempera-

TABLE 1.—*Maximum Temperatures in Hemolytic Streptococcic Sore Throat*

Maximum Temperature

TABLE 1.—*Maximum Temperatures in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Maximum Temperature: Afebrile		99 to 99.9 F.		100 to 100.9 F.		101 to 101.9 F.		102 to 102.9 F.		103 F. and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Antibody response	300	7	2.3	13	4.3	31	10.3	59	19.6	70	23.3	120	40.0
No antibody response	42	0	0.0	3	7.1	7	16.7	9	21.4	10	23.8	13	30.9
Antibody response; tonsils intact	201	5	2.5	9	4.5	20	9.9	39	19.4	48	23.8	80	39.9
Antibody response; tonsils absent	99	2	2.0	4	4.0	11	11.0	20	20.2	22	22.2	40	40.5
Scarlet fever	27	0	0.0	0	0.0	3	11.1	4	14.8	6	22.2	14	51.9
Cervical adenitis													
Absent	62	2	3.2	7	11.3	11	17.7	17	27.4	12	19.3	13	21.0
1 plus	132	3	2.2	7	5.3	14	10.6	24	18.2	29	21.9	55	41.6
2 and 3 plus	148	2	1.3	2	1.3	13	8.8	27	18.2	39	26.4	65	43.9
Pharyngeal exudate													
Absent	126	4	3.2	8	6.3	20	15.9	26	20.6	30	23.8	38	30.2
1 plus	60	0	0.0	3	5.0	6	10.0	17	28.3	19	31.6	15	25.0
2 plus	81	1	1.2	2	2.5	9	11.1	10	12.3	10	12.3	49	60.5
3 plus	75	2	2.7	3	4.0	3	4.0	15	20.0	21	28.0	31	41.3

TABLE 2.—*Duration of Fever in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Duration of Fever, Days: Afebrile		1		2		3		4		5		6 and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Antibody response	300	6	2.0	55	18.3	79	26.3	73	24.3	44	14.7	14	4.6	29	9.7
No antibody response	42	0	0.0	0	21.6	12	28.6	14	33.3	3	7.1	3	7.1	1	2.4
Antibody response															
Tonsils intact	201	5	2.5	40	19.9	49	24.4	52	25.8	30	14.9	5	2.5	20	9.9
Tonsils absent	99	1	1.0	15	15.1	30	30.3	21	21.2	14	14.1	9	9.1	9	9.1
Scarlet fever	27	0	0.0	2	7.4	1	3.7	4	14.8	7	25.9	6	22.2	7	25.9
Cervical adenitis															
Absent	62	2	3.2	18	29.0	16	25.8	11	17.7	6	9.7	5	8.1	4	6.5
1 plus	132	2	1.5	26	19.7	34	25.7	33	25.0	21	15.9	7	5.3	9	6.8
2 or 3 plus	148	2	1.3	20	13.5	41	27.7	43	29.1	20	13.5	5	3.4	17	11.4
Pharyngeal exudate															
Absent	126	3	2.4	32	25.4	31	24.6	24	19.0	24	19.0	4	3.2	8	6.3
1 plus	60	0	0.0	11	18.3	16	26.6	20	33.3	6	10.0	3	5.0	4	6.7
2 plus	81	1	1.2	12	14.8	19	23.5	25	30.9	10	12.3	5	6.2	9	11.1
3 plus	75	2	2.7	8	10.7	25	33.3	19	25.3	7	9.3	5	6.7	9	12.0
Serologic type															
Type 3	33	0	0.0	7	21.2	7	21.2	7	21.2	7	21.2	2	6.1	3	9.1
Type 17	28	0	0.0	4	14.3	2	7.1	3	10.7	11	39.3	1	3.6	7	25.0
Type 19	42	0	0.0	6	14.3	9	21.4	12	28.6	4	9.5	5	11.9	6	14.3
Type 30	20	0	0.0	2	10.0	8	40.0	4	20.0	2	10.0	2	10.0	2	10.0
Type 36	58	2	3.4	12	20.7	22	37.9	14	24.2	4	6.9	2	3.4	2	3.4
Type 46	15	0	0.0	3	20.0	6	40.0	2	13.3	2	13.3	0	0.0	2	13.3
Therapy															
Sulfadiazine	37	1	2.7	5	13.5	8	21.6	7	18.9	5	13.5	2	5.4	9	24.3
Sulfadiazine and penicillin	28	0	0.0	1	3.6	2	7.1	4	14.3	10	35.7	6	21.4	5	17.7
Penicillin, short course	20	0	0.0	1	5.0	5	25.0	8	40.0	1	5.0	0	0.0	5	25.0
Penicillin, long course	13	0	0.0	1	7.7	5	38.5	3	23.0	2	15.4	1	7.7	1	7.7
Salicylates	27	1	3.7	4	14.8	4	14.8	13	48.2	4	14.8	1	3.7	0	0.0

ture fell to normal for one or more days, later to rise again. In others the temperature remained elevated for various reasons. It is, however, obvious that the exhibition of sulfonamide drugs or penicillin cannot be expected to terminate rapidly the febrile phase of acute hemolytic streptococcic sore throat.

The mean duration of fever was four days in sulfonamide-treated patients infected by streptococci moderately resistant to sulfonamide drugs and three and a half days in those in whom the infectious agent was highly susceptible to the antibacterial action of these chemicals. It is clear that the failure of sulfonamide therapy to shorten the febrile course of the disease was not the result of inclusion in the study group of numerous examples of infection by resistant organisms.

Only 1 of the group of 27 patients who received large doses of salicylates throughout their stay in the hospital was febrile for more than four days. This is a statistically significant result if the comparison is made with the first three treatment groups, but not if made with the mean result for all cases.

Among 17 cases in which fever was demonstrated for five days but not longer, there were 7 instances of scarlet fever, 5 examples of an unusually severe local lesion in the throat, 1 case in which a nonsuppurative disorder with arthritis supervened on the second day of illness [9] and 3 cases in which no explanation of the prolonged febrile course was discovered.

Fever persisted for six or more days in 30 cases. This occurred in 5 because of relapse following the premature withdrawal of the use of penicillin and in 2 because of reinfection by a new type of hemolytic streptococcus early in the course of the disease. Severe local suppuration in the throat, either incipient or established peritonsillar abscess or severe cervical adenitis was discovered in 7. The syndrome of uncomplicated scarlet fever was present in 3 cases, and in 3 others suppurative sinusitis was diagnosed. The cause of the prolonged fever was not determined in 4 cases. It was believed in 5 others that a nonsuppurative complication had become established early in the course of the acute illness. These cases will be described elsewhere.[2b]

Duration of Abnormal Signs.—The duration of abnormal signs, including the presence of exudate, edema and redness involving the pharyngeal tissues and tender adenitis of the anterior cervical region, was recorded and the data summarized in table 3. The throat and neck had returned to normal within one to two days in 23.6 per cent and within three to four days in 68.2 per cent of proved cases.

The presence of an antibody response, tonsils or cutaneous rash did not alter the duration of abnormal signs. They did persist for a

9. The administration of salicylates was followed by a prompt return of the temperature to normal.

TABLE 3.—*Duration of Abnormal Physical Signs in Hemolytic Streptococcic Sore Throat*

	No. of Cases	Duration of Abnormal Signs, Days									
		None		1 to 2		3 to 4		5 to 6		7 or More	
		No.	%	No.	%	No.	%	No.	%	No.	%
Antibody response	300	13	4.3	58	19.3	134	44.6	57	19.0	38	12.7
No antibody response	42	3	7.1	5	11.9	21	50.0	8	19.0	5	11.9
Antibody response; tonsils intact	201	9	4.5	27	13.4	85	42.3	52	25.8	28	13.9
Antibody response; tonsils absent	99	4	4.0	31	31.3	49	49.5	5	5.0	10	10.1
Scarlet fever	27	1	3.7	5	18.5	13	48.2	4	14.8	4	14.8
Cervical adenitis											
Absent	62	10	16.1	21	33.9	22	35.5	5	8.1	4	6.5
1 plus	132	4	3.0	34	25.7	62	47.0	22	16.7	10	7.6
2 or 3 plus	148	2	1.3	8	5.4	71	48.0	38	25.6	29	19.6
Pharyngeal exudate											
Absent	126	14	11.1	42	33.3	51	40.5	10	7.9	9	7.1
1 plus	60	1	1.7	14	23.4	33	55.0	9	15.0	3	5.0
2 plus	81	1	1.2	3	3.7	43	53.1	17	21.0	17	21.0
3 plus	75	0	0.0	4	5.3	28	37.3	29	38.7	14	18.7
Therapy											
Sulfadiazine	37	0	0.0	5	13.5	12	32.4	10	27.0	10	27.0
Sulfadiazine and penicillin	28	0	0.0	2	7.1	8	28.6	6	21.4	12	42.9
Penicillin, short course	20	1	5.0	2	10.0	5	25.0	7	35.0	5	25.0
Penicillin, long course	13	0	0.0	0	0.0	4	30.8	5	38.5	4	30.8
Salicylates	27	1	3.7	5	18.5	14	51.9	5	18.5	2	7.4

significantly longer time in cases in which decided cervical adenitis was noted than in those in which it was not. Similarly, there was a direct correlation between the amount of exudate and the persistence of abnormalities. If exudate (2 or 3 plus) was described initially, the throat required more than five days in almost 50 per cent and seven or more days in approximately 20 per cent of cases to return to normal.

Infection by none of the six serologic types resulted in a disease process associated with a significantly long or short duration of abnormalities in the throat and neck. The data on which this statement is based have, therefore, been omitted from the table.

The administration of neither sulfadiazine, penicillin nor a combination of the two shortened the duration of abnormal physical signs. This result was not affected by the degree of resistance of the infectious agent to sulfonamide drugs. The patients treated with these two chemicals did, in fact, have pathologic signs for a significantly longer period than did the group as a whole. The explanation of this fact is probably similar to that offered in regard to the effect of chemotherapy on the duration of fever. It is clear, however, that the use of these drugs in cases of severe conditions is not associated with an immediate return of the diseased tissues to a normal state.

Suppurative Complications.—A variety of suppurative complications followed acute hemolytic streptococcic sore throat during this study. Their nature will be summarized.

Otitis media developed in 5 cases. On three occasions, it was present on or shortly after the patient's admission to the hospital and extremely near the onset of the acute illness. The type of Streptococcus isolated from the throat and ear was the same in these cases. Involvement of the ear occurred on the tenth and nineteenth day of illness in 2 other cases. In both, a strain of hemolytic streptococcus of group G was isolated from the purulent discharge obtained from the ear. Each of these 5 patients received sulfonamide therapy, the response being excellent.

A peritonsillar abscess ruptured in 2 cases before and in 2 after admission to the hospital. The administration of adequate amounts of sulfadiazine failed to bring about resolution of the process in the latter cases. There can be little doubt, however, that the use of this chemical, penicillin or the two agents in combination did prevent the development of tonsillar abscess on a number of occasions.

There were 6 patients in whom suppurative sinusitis appeared to be the cause of prolonged or recurrent fever and disability of unusual duration. An erythrocyte sedimentation rate of more than 25 mm. per hour was discovered three weeks after the onset of the initial illness in 6 additional cases. No definite clinical evidence of a disease process was present in any of these men, but cultures of material from the nose

which were strongly positive for organisms at the time of follow-up examination suggested that the continuing reaction of the tissues was the result of infection of the paranasal sinuses. A similar process was doubtless present in many other cases but cleared spontaneously or failed to increase or prolong disability and was therefore not diagnosed. Certain aspects of this problem were studied in this same group of patients by Hamburger, Green and Hamburger.[10]

The erythrocyte sedimentation rate also remained elevated for three or more weeks in 9 additional patients in whom the initial suppurative process in the throat had been unusually severe. No evidence of disability or continuing illness was demonstrable in any of these patients at the follow-up examination.

The prompt recovery in 18 cases not previously mentioned was hampered by the occurrence of a clinical relapse following the discontinuance of therapy consisting of penicillin alone or followed by sulfadiazine. This subject has been considered fully elsewhere.[6]

The convalescence of a small group of patients was complicated by reinfection with a new type of group A hemolytic streptococcus associated with the development of frank clinical signs of disease. In others a similar event occurred, but only alterations in the results of laboratory tests indicated that a new infection had supervened. It has been noted previously that reinfection may be related to the development of nonsuppurative complications.[2a] It is more appropriate, therefore, to consider these cases in the paper devoted to the latter disorders.

CLINICOPATHOLOGIC OBSERVATIONS

Erythrocyte Sedimentation Rate.—The measurement of the erythrocyte sedimentation rate is an accepted method for the estimation of the severity and duration of the reaction of the tissue to infection by a variety of micro-organisms. The rates were determined initially in 342 and three weeks later in 299 of these cases of hemolytic streptococcic sore throat. The information obtained has been exhaustively analyzed and the effect of various clinical manifestations of the disease evaluated.

The values obtained during the initial phase of the disease have been described previously.[1] It was noted that the rate was greater than 20 mm. per hour in 70.8 per cent, greater than 30 mm. per hour in 50.1 per cent, greater than 40 mm. per hour in 32.7 per cent and greater than 50 mm. per hour in 19.4 per cent of the proved cases. No correlation existed between the presence of an antibody response, tonsils or a cutaneous rash and the initial erythrocyte sedimentation rate.

10. Hamburger, M.; Green, M. J., and Hamburger, V. G.: The Problem of the Dangerous Carrier of Hemolytic Streptococci: I. Number of Hemolytic Streptococci Expelled by Carriers with Positive and Negative Nose Cultures, J. Infect. Dis. **77**:68, 1945.

The results of other analyses made since that time are presented in table 4. The frequency of occurrence of rates greater than 40 mm. per hour on the initial examination and 30 mm. per hour on the follow-up examination have been used as indexes for study. If any correlation

TABLE 4.—*Initial and Follow-up Erythrocyte Sedimentation Rates in Hemolytic Streptococcic Sore Throat*

	Initial Erythrocyte Sedimentation Rate			Erythrocyte Sedimentatinn Rate on the 19th to 25th Day		
	No. Studied	No. with Rate Greater Than 40 Mm./Hr.	Per Cent with Rate Greater Than 40 Mm./Hr.	No. Studied	No. with Rate Greater Than 30 Mm./Hr.	Per Cent with Rate Greater Than 30 Mm./Hr.
Antibody response	294	96	32.7	262	51	19.4
No antibody response	41	8	19.5	37	3	8.1
Antibody response; tonsils intact	198	66	33.3	174	33	18.9
Antibody response; tonsils absent	96	30	31.2	88	18	20.4
Scarlet fever	26	7	26.9	26	11	42.3
Cervical adenitis						
Absent	63	15	23.8	56	5	8.9
1 plus	128	40	31.2	116	21	18.1
2 or 3 plus	144	49	34.1	127	28	22.0
Pharyngeal exudate						
Absent	123	38	30.9	110	18	16.4
1 plus	59	21	35.6	50	12	24.0
2 plus	81	24	29.6	70	12	17.1
3 plus	72	21	29.2	69	12	17.3
Maximum temperature						
Afebrile to 99.9 F	23	4	17.4	21	1	4.8
100.0 to 100.9 F	38	10	26.3	35	3	8.5
101.0 to 101.9 F	65	12	18.4	57	6	10.6
102.0 to 102.9 F	77	32	41.6	69	15	21.7
103.0 F. and over	132	46	35.1	117	29	24.7
Duration of fever						
1 day or less	70	14	20.0	60	7	11.6
2 days	88	22	27.3	78	9	11.5
3 days	86	25	29.1	78	14	17.9
4 days	46	24	52.1	40	8	20.0
5 days	16	5	31.2	16	6	37.5
6 days or more	29	12	41.3	27	10	37.0
Serologic type						
Type 3	33	10	30.4	31	6	19.2
Type 17	26	14	53.8	26	5	19.2
Type 19	41	19	46.3	37	5	13.5
Type 30	20	9	45.0	20	8	40.0
Type 36	56	13	23.2	48	10	20.7
Type 46	15	7	46.7	14	4	28.6
Therapy						
Sulfadiazine	34	19	55.9	33	6	18.2
Sulfadiazine and penicillin	28	11	39.2	28	6	21.4
Penicillin, short course	19	3	15.8	18	7	38.9
Penicillin, long course	13	4	30.8	13	2	15.4
Salicylates	27	7	25.9	24	3	12.5

appeared to exist in any category, further examination was made of the relationship of the occurrence of slower rates to the clinical manifestation in question. The limitations of space forbid the presentation of all these data in tabular form.

There was no relationship between the severity of cervical lymphadenitis, the amount of exudate in the throat, the maximum temperature,

the duration of fever or the serologic type of Streptococcus and the occurrence of extremely rapid initial erythrocyte sedimentation rates. None of the differences discernible in the table are greater than those to be expected on the basis of chance.

The erythrocyte sedimentation rate was greater than 20 mm. per hour in 30.8 per cent and greater than 30 mm. per hour in 19.4 per cent of proved cases nineteen to twenty-five days after the onset of the illness. The data presented in the table suggest that the rates at this time were more prolonged, with increasing severity of cervical adenitis, greater height of maximum temperature, more prolonged febrile course and the presence of a cutaneous rash or of an antibody response. Although these associated variations would not be unexpected, none deviates sufficiently from the mean to be of definite significance. It is possible that the stated trends are real and could be confirmed by the study of a larger group of cases.

TABLE 5.—*Relationship Between Initial and Follow-up Erythrocyte Sedimentation Rates in Hemolytic Streptococcic Sore Throat*

Initial Erythrocyte Sedimentation Rate	No. Done	Erythrocyte Sedimentation Rate on 18th to 25th Day									
		Less than 9		10 to 19		20 to 29		30 to 39		40 and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%
Less than 9	29	26	89.8	1	3.4	1	3.4	0	0.0	1	3.4
10 to 19	61	48	78.6	8	13.1	4	6.5	0	0.0	1	1.6
20 to 29	62	35	56.5	14	22.6	5	8.1	4	6.4	4	6.4
30 to 39	51	24	47.0	9	17.6	7	13.7	4	7.8	7	13.7
40 to 49	38	13	34.2	10	26.3	5	13.1	6	15.8	4	10.5
50 and over	53	8	15.1	13	24.5	11	20.7	8	15.1	13	24.5

It is obvious from an inspection of the table that the erythrocyte sedimentation rate at the end of three weeks was not influenced by the amount of exudate in the throat, the presence of tonsils, the serologic type of infecting Streptococcus, the utilization of antibacterial chemotherapy or the administration of salicylates.

The relationship of the initial erythrocyte sedimentation rate to that obtained approximately three weeks later is indicated by the data presented in table 5. There was a direct correlation between the two values. The follow-up rate was normal (less than 20 mm. per hour) in only 48.5 per cent of cases in which the initial rate was 40 mm. per hour or more. Conversely, if the initial rate was within normal limits, the follow-up rate was also within normal limits in 92.0 per cent of cases. It is important to point out that the follow-up rates were more rapid than the initial in a considerable number of cases. Some of these patients suffered from nonsuppurative complications and will be described elsewhere.

Total Leukocyte Count.—The total leukocyte count was determined on approximately the second day of illness in 342 cases. The data are

presented in table 6. The count was greater than 9,000 per cubic millimeter in 76.9 per cent, greater than 13,000 in 49.1 per cent and greater than 16,000 in 26.7 per cent of proved cases. The presence of an antibody response, tonsils or cutaneous rash did not significantly affect these values. If the counts below 16,000 cells per cubic millimeter are considered, certain trends are observed which are not of definite statistical significance. Thus, the total count is higher with increasing severity

TABLE 6.—*The Initial Total Leukocyte Count in Hemolytic Streptococcic Sore Throat*

		Initial Leukocyte Count in Thousands							
		Less than 9,000		10,000 to 12,900		13,000 to 15,900		16,000 and Up	
	No. of Cases	No.	%	No.	%	No.	%	No.	%
Antibody response	299	69	23.1	83	27.8	67	22.4	80	26.7
No antibody response	42	14	33.3	11	26.2	12	28.6	5	11.9
Antibody response; tonsils intact	201	43	21.4	53	26.4	49	24.4	56	27.8
Antibody response; tonsils absent	98	26	26.5	30	30.6	18	18.7	24	24.5
Scarlet fever	27	5	18.5	6	22.2	6	22.2	10	37.0
Cervical adenitis									
Absent	62	22	35.5	22	35.5	8	12.9	10	16.1
1 plus	131	33	25.2	40	30.6	35	26.7	23	17.5
2 or 3 plus	148	29	19.6	32	21.6	36	24.4	51	34.4
Pharyngeal exudate									
Absent	126	42	33.3	39	30.9	25	19.8	10	15.9
1 plus	59	10	16.9	19	32.2	14	23.7	16	27.1
2 plus	81	19	23.5	17	21.0	22	27.2	23	28.4
3 plus	75	13	17.3	19	25.3	18	24.0	25	33.3
Maximum temperature									
Afebrile to 99.9 F	23	8	34.8	9	39.1	5	21.7	1	4.4
100.0 to 100.9 F	38	16	42.1	10	26.3	9	23.7	3	7.9
101.0 to 101.9 F	68	21	30.9	18	26.5	10	14.7	19	27.9
102.0 to 102.9 F	80	13	16.2	26	32.5	24	30.0	17	21.3
103.0 F. and up	132	26	19.7	31	23.5	31	23.5	44	33.3
Duration of fever									
Afebrile to 1 day	70	26	37.2	24	34.3	16	22.9	4	5.7
2 days	91	32	35.1	26	28.6	20	22.0	13	14.3
3 days	86	12	13.9	22	25.6	23	26.7	29	33.8
4 days	47	5	10.6	14	29.8	11	23.4	17	36.2
5 days	17	4	23.5	2	11.7	5	29.4	6	35.3
6 days and up	30	5	16.7	6	20.0	4	13.3	15	50.0
Therapy									
Sulfadiazine	37	11	29.7	10	27.0	5	13.5	11	29.7
Sulfadiazine and penicillin	28	5	17.8	5	17.8	1	3.6	17	60.7
Penicillin, short course	20	4	20.0	3	15.0	5	25.0	8	40.0
Penicillin, long course	13	2	15.4	2	15.4	4	30.8	5	38.4
Salicylates	27	2	7.4	9	33.3	9	33.3	7	25.9

of adenitis, amount of exudate, height of maximum temperature and duration of fever. When the counts above 16,000 per cubic millimeter are analyzed, the trends just mentioned are emphasized and become significant. If the maximum temperature was greater than 101 F. or if fever was to persist for more than three days, the number of extremely high counts was strikingly increased, as it was in patients with severe cervical adenitis or large amounts of exudate in the throat. No correlation between the serologic type of infecting Streptococcus and the total initial leukocyte count was discovered, and the data have been omitted from the table.

The analysis of the leukocyte count, obtained about nine days after the onset of the acute illness in 306 cases, was not particularly illuminating, since at this time there had been only a moderate return of the values to normal and all the relationships previously noted were maintained at slightly lower levels. That this should have been the case is remarkable when the data presented in table 7 are evaluated. In it the initial total leukocyte count is compared with the count obtained at about nine days in the same patients. In many cases the count, if elevated, returned toward normal, but on others, making up more than one third of the whole group, there was a moderate to pronounced

TABLE 7.—*Relationship Between Initial Leukocyte Counts and Those Obtained on the Eighth to Tenth Day of Hemolytic Streptococcic Sore Throat*

		Leukocyte Count on 8th to 10th Day							
		Less than 9,000		10,000 to 12,900		13,000 to 15,900		16,000 and Up	
Initial Leukocyte Count	No. Done	No.	%	No.	%	No.	%	No.	%
9,000 or less	74	37	50.0	17	23.0	9	12.2	11	14.8
10,000 to 12,900	111	28	25.2	31	27.9	33	29.7	19	17.1
13,000 to 15,900	64	9	14.0	21	32.8	19	29.7	15	23.4
16,000 and up	56	4	7.1	12	21.4	10	17.9	30	53.6

increase in the total number of leukocytes. An explanation for this phenomenon occurring in a large number of patients, most of whom were recovering rapidly from their illness, is not immediately forthcoming.

Neither any of the antibacterial therapeutic regimens nor the administration of sodium salicylate significantly reduced the frequency of occurrence of elevated leukocyte counts at the second examination.

BACTERIOLOGIC OBSERVATIONS

The results obtained on the initial cultures of material from the nose and throat in this group of cases of hemolytic streptococcic sore throat, including the distribution of the isolated strains among the various Lancefield types, have been described.[11] The natural history of the carrier state of group A hemolytic streptococci and the effect on it of chemotherapy will be recounted at this time. The essential data are enumerated in table 8. Approximately 75 per cent of the patients with proved infection remained pharyngeal carriers of hemolytic streptococci on the eighth to tenth day of the illness. The incidence of nasal carriers had decreased from about 65 to 28 per cent at this time. These rates at this stage of the disease were similar whether an antibody response, tonsils or a cutaneous rash had or had not been present.

11. Rantz, L. A.; Rantz, H. H.; Boisvert, P. J., and Spink, W. W.: Streptococcic and Nonstreptococcic Disease of the Respiratory Tract: Epidemiologic Observations, Arch. Int. Med. **77**:121 (Feb.) 1946.

TABLE 8.—*Course of the Carrier State in Hemolytic Streptococcic Sore Throat*

	Initial Cultures, Nose			Cultures at 8 to 10 Days						Cultures at 19 to 25 Days					
				Throat			Nose			Throat			Nose		
	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive	No.	No. Positive	% Positive
Antibody response	289	190	65.7	267	200	75.0	240	68	28.3	222	146	65.8	227	52	22.9
No antibody response	39	19	48.7	36	27	75.0	32	14	43.7	36	16	44.4	35	4	11.4
Antibody response															
Tonsils intact	193	122	63.2	177	135	76.3	160	44	27.5	150	108	72.0	150	33	22.0
Tonsils absent	96	68	70.9	90	65	72.2	80	24	30.0	72	38	52.8	77	19	24.7
Scarlet fever	25	19	76.0	15	12	80.0	8	3	37.5	9	5	55.6	7	4	57.1
Serologic type															
Type 3	33	19	57.5	30	11	36.7	32	5	15.6	29	9	31.0	30	2	6.7
Type 17	26	18	69.3	27	22	81.5	23	11	47.8	19	13	68.4	20	4	20.0
Type 19	40	24	60.0	39	33	84.6	32	10	31.2	34	30	88.3	35	12	34.3
Type 30	20	14	70.0	18	16	88.9	16	10	62.5	8	8	100.0	12	5	41.7
Type 36	53	39	73.6	46	35	76.1	39	12	30.7	47	29	61.7	48	10	20.8
Type 46	15	11	73.4	15	11	73.4	14	4	28.5	11	7	63.7	12	2	16.6
Therapy															
None	209	122	58.5	189	152	80.1	171	58	33.9	161	97	60.2	169	30	17.7
Sulfadiazine	34	27	79.5	32	22	68.8	28	7	25.0	28	20	71.4	29	7	24.1
Sulfadiazine and penicillin	27	19	70.4	28	20	71.4	23	5	21.7	21	14	66.6	25	6	24.0
Penicillin, short course	19	14	73.7	20	20	100.0	17	6	35.3	17	13	76.5	17	7	41.1
Penicillin, long course	12	7	58.4	12	4	33.3	11	2	18.2	10	4	40.0	11	2	18.2
Salicylates	27	20	74.0	22	14	63.6	22	4	18.2	21	15	71.5	20	4	20.0
Sulfadiazine or sulfadiazine after penicillin															
Sulfonamide-sensitive organisms	23	18	78.2	22	16	72.7	19	4	21.0	19	15	78.9	20	6	30.0
Sulfonamide-resistant organisms	32	24	75.0	32	23	71.9	22	7	31.8	26	19	73.1	28	7	25.0

Only a slight diminution in the number of pharyngeal and nasal carriers occurred during the following two weeks. Hemolytic streptococci were recovered from the throat less frequently at the end of three weeks if the tonsils had been removed. The absence of these organs did not affect the rate of nasal carriers.

The occurrence of group A carriers was evaluated in relationship to the serologic types of the etiologic agent, and the results are presented in table 8 because significant information was obtained. Pharyngeal carriers were less frequently discovered at eight to ten and at nineteen to twenty-five days when the etiologic agent was a strain of type 3.

The incidence of cultures of material from the nose yielding pathogens also varied with the serologic type of the infecting organism. Differences in the rate of nasal carriers, which had begun to manifest themselves at the end of the first week, were definite two weeks later in that there were less patients with infection of type 3 and more with infection of type 19 still harboring hemolytic streptococci in the nose than were members of the whole group, or those infected by the other four types. These differences are not the result of the use of any antibacterial chemical and are statistically significant.

The effect of antibacterial chemotherapy on the state of the carriers of group A hemolytic streptococci has been summarized previously.[12] The data on which this report was based are presented in the last eight lines of table 8. Only brief comment on this matter is necessary, since administration of neither sulfadiazine nor penicillin, alone or in combination, resulted in a significant diminution in the incidence of pharyngeal or nasal carriers of group A streptococci. The persistence of hemolytic streptococci in the upper air passages of all sulfonamide-treated patients was analyzed with reference to the sensitivity of the etiologic agent to sulfonamide drugs. The frequency of occurrence of pharyngeal and nasal carriers at the various intervals in the two groups was similar. It is unlikely, therefore, that the failure of sulfadiazine to eliminate hemolytic streptococci from the nose and throat in these cases was the result of the presence of organisms moderately resistant to sulfonamide drugs as the cause of many of the infections. It should be noted that these organisms were permanently eradicated from the nasopharynges of at least 7 men who received the "long course" of penicillin.

COMMENT

Only a brief discussion of this purely factual description of the course of acute hemolytic streptococcic sore throat in young men is necessary. The essential data are presented in tables and brief comments made with special reference to the results of statistical analyses that had been car-

12. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Chemotherapy and the Hemolytic Streptococcus Carrier State, Bull. U. S. Army M. Dept. **5**:662, 1946.

ried out. A detailed narrative description of all the observations was impossible because of the limitations of space.

The disease had a variable course, as was to be expected. The temperature rose to 102 F. or more in 63.3 per cent and remained elevated for not more than three days in 71.0 per cent of all cases in which infection was proved by the presence of an antibody response. All physical signs had disappeared from the throat and neck within four days in 68.2 per cent of the same group of cases. A prolonged febrile course was usually associated with the presence of a cutaneous rash, of an unusually severe suppurative process in the throat or a suppurative complication. In a few patients, the early supervention of a nonsuppurative complication prolonged the period of disability.

The severity and frequency of occurrence of the clinical manifestations of the disease were extensively correlated with one another and with the laboratory observations. It was anticipated that the magnitude of the involvement of the pharyngeal tissues, as estimated by palpation of the neck and inspection of the pharynx, would be closely related to the degree and duration of fever, but this was not the case. Significantly lower temperatures were noted in patients without tender cervical adenitis, but the height of temperature did not reflect the amount of exudate in the throat. The febrile phase of the illness was of greater length when a cutaneous rash was present but was not affected by the magnitude of other physical abnormalities. The persistence of abnormal physical signs was directly correlated with the extent of the initial lesion in the throat.

The erythrocyte sedimentation rate was usually more rapid than normal on the second or third day of acute hemolytic streptococcic sore throat. The magnitude of this abnormality was not well correlated with the usual clinical manifestations used to measure the severity of the infectious process. Neither the height of the maximum temperature, the duration of fever, the degree of estimated abnormality of the pharyngeal tissues nor a cutaneous rash could be shown to be significantly associated with the initial erythrocyte sedimentation rate. Later, when this laboratory procedure was carried out during convalescence, there was a relationship between the severity of the previously observed illness and the erythrocyte sedimentation rate which was more nearly significant and may well measure an actual correlation.

The number of total leukocytes varied with the severity of the demonstrable suppurative process in the throat but most strikingly with the height of maximum temperature and duration of the febrile illness.

The lack of statistical correlation between the frequency of occurrence, severity and degree of abnormality of the various clinical signs and laboratory procedures strongly suggests that these manifestations of the infectious process do not have a common pathogenesis. Thus the product or function of the hemolytic streptococcus that stimulates and

maintains fever does not appear to be the same as that which incites the formation of the lesion in the pharyngeal tissues. Leukocytosis was most actively provoked by the fever-producing agent. No definite relationship between either factor and the erythrocyte sedimentation rate was discovered, suggesting that a third pathologic mechanism was operative.

It is not the purpose of this paper to elucidate in detail the pathogenesis of the various manifestations of hemolytic streptococcic sore throat. The information just presented suggests that the infectious process is complex.

Certain of the manifestations of the disease must be the result of the direct toxic action of the metabolic products of the multiplying organism acting locally or systemically. Others may well result from an altered or "allergic" reaction of the tissues of the host to these products as the result of previous infection by the hemolytic streptococcus. Evidence has been presented which indicates that the cutaneous rash may result from the action of such a mechanism.[13] Another group of investigators has suggested that the observed differences between the natural history of hemolytic streptococcic respiratory disease in infants and in older children and adults are the consequence of a reaction of the tissue altered in the latter by earlier exposure to the organism.[14]

A variety of therapeutic regimens, involving the administration of varying amounts of penicillin, alone or in combination with sulfadiazine or the latter drug alone, were instituted. The number of cases in each treatment group is not large, and no true controls are available, since the most severely ill patients usually received antibacterial therapy. The evidence presented herein demonstrates that none of the several regimens sharply terminated the febrile illness, induced a dramatic resolution of the suppurative lesion in the throat or led to an unusually rapid return to normal of the various laboratory tests. It is possible that suppurative complications were prevented in certain cases, but this may only be inferred. This analysis, which indicates the relative inefficacy of the chemotherapy of hemolytic streptococcic sore throat, is in accord with one made previously using part of these data.[6]

The natural history of sore throat caused by each of six serologic types of group A hemolytic streptococci was analyzed and compared. Biologic differences existed between strains of the various types. In spite of this fact, the signs and symptoms of the initial phase of the infection, its course and the degree of abnormality of the various

13. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Dick Test in Military Personnel with Special Reference to the Pathogenesis of the Skin Reaction, New England J. Med. **39**:235, 1946.

14. Bearg, P. A.; Boisvert, P. J.; Darrow, D. C.; Powers, G. F., and Trask, J. D.: "Streptococcosis" and "Streptococcic Fever," Am. J. Dis. Child. **62**:431 (Aug.) 1941.

laboratory tests were similar, regardless of the type of etiologic agent. Infection by four of the types (3, 17, 19, and 30) was associated with a cutaneous rash in certain persons, and the febrile course of the illness was in these circumstances more prolonged.

The information obtained during this study permits a description of the first three weeks of the carrier state of group A hemolytic streptococci in young adults. The organisms were isolated from the pharynxes of 99 per cent and from the noses of 65 per cent of these patients at the onset of the illness. One week later 75 per cent were proved to be pharyngeal and 28 per cent nasal carriers. Only an extremely slight diminution in the number of carriers occurred during a subsequent two weeks' period of observation. A persistent pharyngeal carrier state was established less often in persons in whom the tonsils had been removed. The absence of these organs had no effect on the occurrence of nasal carriers. Strains of type 3 persisted in the throat and nose for a shorter and strains of type 19 for a longer period than did those of other types.

Persons harboring hemolytic streptococci in the upper air passages, particularly the nose,[10] often transmit these organisms to susceptible human beings. It is worth while, therefore, to emphasize the fact that a large number of these infected men became persistent pharyngeal and nasal carriers and that none of the antibacterial therapeutic regimens was effective in the elimination of the organism from the throat and nose.

SUMMARY

1. The natural history of the acute suppurative phase of group A hemolytic streptococcic sore throat in young adults has been described.

2. The degree and duration of fever and the initial erythrocyte sedimentation rate were poorly correlated with the degree of physical abnormality of the throat and neck.

3. A more prolonged febrile illness occurred if a cutaneous rash was present.

4. The initial leukocyte count varied with the severity of the acute disease.

5. A rash occurred only when the infecting Streptococcus was of type 3, 17, 19 or 30. The disease caused by six serologic types was otherwise similar.

6. The first three postinfectious weeks of the group A carrier state have been described.

7. Several therapeutic regimens, involving the administration of sulfadiazine and penicillin, alone and in combination, were utilized. None effectively terminated the disease or consistently eradicated the hemolytic streptococcus from the nose and throat.

BRONCHIOGENIC ADENOMA

Benign Tumor of the Bronchus

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WHAT IS known today as polypoid adenoma of the bronchus was observed and recorded by Laennec in his treatise on ausculation. Laennec [1] wrote:

> It is rare for polypoid excrescences to develop on the mucous membrane of the bronchi; only three examples are known to me. It seems that these excrescences are of the type of vascular polyps of the nose, ears and uterine cervix, that is to say, they are formed by tissue analogous to the mucous membrane containing small serous cysts.

The literature contains a reference to Mueller,[2] who accidentally found an instance of the condition at autopsy but ignored completely Laennec's observation. After the appearance of Mueller's article the disease was identified by pathologists, and after the introduction of the bronchoscope it was recognized in the clinic. Chiefly American and British physicians are responsible for the interest evinced in the disease. Patterson [3] and Yankauer [4] were among the first to report cases. Patterson found 26 cases in the available literature, in 10 of which the disease was disclosed at necropsy; in the remaining 16 it had been diagnosed bronchoscopically. Kramer [5] outlined clinical features, bronchoscopic treatment and the use of radon seeds. Kramer's studies were further developed by Wessler and Rabin,[6] but particularly important were the extensive studies by Chevalier Jackson.[7]

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1. Laennec, R.: Traité de l'auscultation mèdiate et des maladies des poumons et du cœur, ed. 3, Paris, J. S. Chaudé, 1831, vol. 1, p. 250.

2. Mueller, H.: Zur Entstehungsgeschichte der Bronchialerweiterungen, Halle, A. Busch, 1882.

3. Patterson, E. J.: Benign Bronchial Neoplasms, Arch. Otolaryng. **12**:739 (Dec.) 1930.

4. Yankauer, S.: Laryngoscope **39**:649, 1929.

5. Kramer, R.: Ann. Otol., Rhin. & Laryng. **39**:689, 1930.

6. Wessler, H., and Rabin, C.: Am. J. M. Sc. **183**:164, 1932.

7. Jackson, C., and Jackson, C. L.: Benign Tumors of Trachea and Bronchi, with Especial Reference to Tumor-Like Formations of Inflammatory Origin, J. A. M. A. **99**:1747 (Nov. 19) 1932.

Morlock and Pinchin,[8] Foster-Carter,[9] Kramer and Som[10] and Lowry and Rigler[11] estimated that adenoma of the bronchus is the commonest benign bronchial tumor and that it occurs in about 6 per cent of all bronchial neoplasms. Of 243 cases of bronchiogenic tumors studied bronchoscopically in fifteen years, Clerf and Bucher[12] observed adenomas in 35, or 12 per cent. It is significant that in spite of their accessibility in barely one half of the cases was the condition diagnosed during life.

PATHOLOGY

The adenoma starts in the mucosa or submucosa of a large bronchus, whose diameter is at least 10 mm. The notion that it always spreads in the direction of the bronchial lumen, leaving the parenchyma of the lung intact, has been contradicted by recent observations. It appeared that in the majority of cases the tumor advances in two directions—toward the bronchial lumen and toward the parenchyma of the lung. In its bidirectional advance it ultimately formed a "pouch" divided by a purse string–like constriction at the point of origin in the wall of the bronchus. It was surrounded by a capsule of connective tissue, which was covered in the endobronchial segment by the bronchial mucosa.

Some observers identified still another type, the intramural, said to be strictly confined to the bronchial wall which it infiltrated.

In the early stages the adenoma appears as a wartlike prominence, usually firm and sessile; in the advanced stage it becomes pedunculated, sometimes assuming a pyriform shape, suspended and hanging by its constricted neck like a clapper of a bell. Its tendency to project upward is due to the expulsive effort of coughing.

Early observers considered bronchiogenic adenoma a slow-growing, benign new growth. The opinion of recent investigators is divided between those who stated that it is a benign neoplasm and those who considered it as potentially malignant. Adams and his associates[13] found in 1 of their cases a metastasis in the vertebral bone marrow, in another in the bronchial lymph node and in still another in the mediastinal lymph node and the liver. In Anderson's[14] case, tumor cells

8. Morlock, H. V., and Pinchin, A. J. S.: Brit. M. J. **1**:911, 1933.
9. Foster-Carter, A. F.: Quart. J. Med. **10**:139, 1941.
10. Kramer, R., and Som, M. L.: Ann. Otol., Rhin. & Laryng. **44**:861, 1935.
11. Lowry, T., and Rigler, L. G.: Radiology **43**:213, 1944.
12. Clerf, L. H., and Bucher, C. J.: Ann. Otol., Rhin. & Laryng. **51**:836, 1942.
13. Adams, W. E.; Steiner, P. E., and Bloch, R. G.: Malignant Adenoma of Lung: Carcinoma-like Tumors with Long Clinical Course, Surgery **11**:503 (April) 1942.
14. Anderson, W. M.: Bronchial Adenoma with Metastasis to Liver, J. Thoracic Surg. **12**:351 (April) 1943.

extended between the bronchial cartilages and involved the entire thickness of the bronchial wall; they invaded several perivascular and peribronchial lymphatic vessels near the periphery of the growth and also the liver.

The occurrence of metastases, while extremely rare, is nevertheless puzzling, because the histologic structure of the tumor is that of a benign new growth. Its cells are uniformly the size of a lymphocyte or a plasma cell, with a somewhat oval nucleus and a narrow rim of cytoplasm. The arrangement of the cells is orderly, usually forming tubules without lumens or with barely noticeable lumens. The stroma is delicate, containing occasional slits lined with endothelial-like cells. In some cases of advanced metastases the stroma becomes dense, showing areas of ossification. Mitotic figures are rarely if ever found even in the adenomas which have metastasized to distant organs. Likewise, the infiltration of the stroma with lymphocytes, so characteristic of malignant tumors, is entirely lacking in bronchiogenic adenoma. Finally, adenomas are as a rule surrounded by a connective tissue capsule.

It is significant that the metastases found in a few cases were minute, sometimes microscopic and confined to only one or two organs, and they occurred in persons whose disease was of many years' duration. In cancer, it has been noticed, metastases often occur in inverse ratio to the tempo of the new growth; the slower the growth, the more widespread are the metastases.

Malignancy involves multiple factors, such as recurrence of growth after removal, metastases, radiosensitivity and constitutional symptoms, to mention but a few. Patients with bronchiogenic adenoma displayed none of the characteristics associated with malignant disease. Their ailment was protracted over many years, and the metastases were minute and few and were discovered accidentally at the postmortem examination. After the complete removal of the tumor the patients recovered.

At the Massachusetts General Hospital, of 175 cases of pulmonary tumors bronchial adenomas were found in 17, or 10 per cent. Fifteen (88 per cent) of the 17 patients were living and asymptomatic from three to five years later. Of 155 patients with carcinoma of the bronchus, only 5, or 3 per cent, were alive for the same period. Of 28 patients in whom the carcinoma had been removed surgically, only 3 (11 per cent) have a chance of five years' survival, while, of 11 patients in whom the adenoma had been removed surgically, 10 (90 per cent) were living and none revealed signs of malignant disease.

The histogenesis of the adenoma was traced by some observers to the cells lining the ducts of the bronchial glands and by others to oncocytes, epithelial cells resembling those of the organ in which they are found and

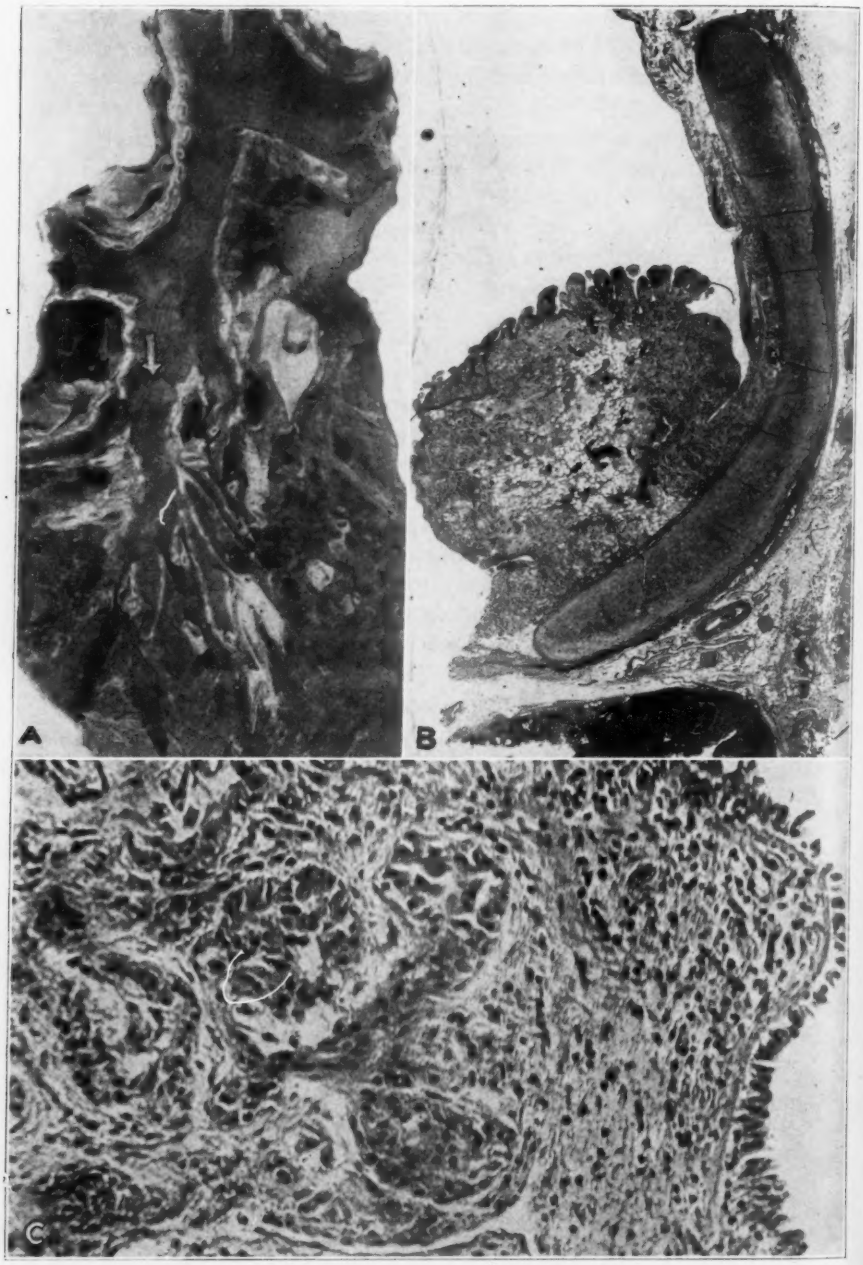

Fig. 1 (case 1).—*A*, polypoid endobronchial adenoma protruding into the bronchial lumen (arrow). *B*, cut surface of the tumor. *C*, histologic structure.

differing from them in size and in the presence of cytoplasmic acidophilic granules and deeply stained pyknotic nuclei (Stout [15]).

Womack and Graham [16] stated that bronchiogenic adenomas have their origin in anlages that have failed to develop normally. They stated: "These tumors resemble fetal pulmonary tissue. . . . they result from the failure of embryonic bronchial buds to develop into normal [bronchial] structures." In their opinion there exists a similarity of behavior and "in some respects" of origin of bronchial adenomas to the mixed tumors of the parotid gland, and as such the bronchial tumors are designated as mixed tumors of the lungs.

There are two possible sources for the origin of bronchial adenomas: (1) the bronchial mucous glands and (2) the basal cells of the bronchial mucous membrane. In the case of involvement of the mucous glands the tumor cells resemble the secreting cells of the gland—large polygonal cells with a wide rim of cytoplasm containing acidophilic granules and deeply stained nuclei. A case of this variety is herein presented.

CASE 1.—*History.*—The past history of the patient, aged 57, was irrelevant, and his present illness was that of hypertension and hypertensive cardiac disease, to which he succumbed. At necropsy the adenoma was found in the lower part of the left bronchus, at the point of its division into the upper and lower branches. It represented a round, smooth, grayish polypoid elevation protruding into the bronchial lumen, constricted at the base. It measured 1 cm. in diameter (fig. 1 *A* and *B*). Under the microscope it was composed of clustered alveoli made up of large polygonal cells with a finely granular acid-staining cytoplasm and a round or oval nucleus (fig. 1 *C*). The similarity of these cells to the aforementioned oncocytes is noteworthy. The stroma is made up of loose edematous connective tissue and numerous thin-walled channels filled with red cells. The tumor is surrounded by a collagenous capsule covered by a layer of bronchial epithelium undergoing metaplastic transformation.

It would appear that in this case the polypoid "excrescence," to use Laennec's term, took origin in the cells of the mucous glands.[17] However, by far the commoner source for the genesis of these tumors is the basal cells of the bronchial mucosa. These cells, found in clusters interspersed between the columnar and the mucous (goblet) cells, represent a dynamic unit, playing a role in regenerative and fibrogenic processes taking place in the lung. That this cell is the mother cell for bronchiogenic carcinoma is now universally accepted.[18]

15. Stout, A. P.: Cellular Origin of Bronchial Adenoma, Arch. Path. **35**:803 (June) 1943.

16. Womack, N., and Graham, E. A.: Mixed Tumors of the Lung, Arch. Path. **26**:165 (July) 1938.

17. Fried, B. M.: Adenoma of Bronchial Mucous Glands, Arch. Otolaryng. **20**:375 (Sept.) 1934.

18. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932, p. 27.

The cells which make up bronchiogenic adenoma closely resemble basal cells. It is often possible to trace a connection between these cells and the tumor, although failure to find such a liaison does not invalidate the assertion of such a genetic relationship. Thus, it is well established that carcinoid tumors of the bowel originate from the epithelial cells of the Lieberkühn's crypts by cellular sprouting; however, with the advance of the tumor the connecting bridge vanishes.

DIAGNOSIS

In another section appears the statement that bronchiogenic adenoma has been compared with an iceberg, since only part of it is visible on the surface, and, like an iceberg, its advance is extremely slow. Cases are on record in which symptoms existed for decades. That there is a "preclinical" asymptomatic period goes without saying. Early complaints are usually those of a cough productive of mucoid sputum occasionally streaked with blood. The ominous symptom, however, is the occurrence of hemoptysis, which is characterized by abruptness and copiousness. Carcinoma of the lung, too, produces hemorrhages, but they are rarely abundant. The source of bleeding has been traced to ruptured thin-walled blood vessels which abound in polypoid adenomas. In the performance of biopsies it has been noticed that, unlike bronchiogenic carcinoma, adenoma bleeds profusely, the bleeding reaching at times a dangerous point.

In the past the disease had been diagnosed as tuberculosis, and patients were treated accordingly. Cases 2 and 3 are illustrative. Further in its course the symptomatology is dominated by the increasing size of the endobronchial growth, causing occlusion of the bronchial lumen. It is well to consider two phases: (1) preobstructive or partially obstructive and (2) obstructive.

In the first phase, in addition to cough and bleeding, a wheeze in the chest is heard on auscultation (heard best with the patient's mouth open), often by the patient himself. Not infrequently there is soreness of the chest on the side of the affected bronchus. Although not completely shut off from the ingress of air, the lung loses its usual resistance and readily becomes a prey to infection; the patients suffer sporadically from "colds," with elevation of temperature (recurrent "pneumonia"). Bronchial stenosis, whether caused by a tuberculous infection or a malignant or benign neoplasm, often induces stagnation, with the formation of a thick mucopurulent secretion plugging the bronchial lumen. The bouts of fever, lasting as long as this condition persists, are usually due to the obstruction. When the plug is removed spontaneously or with the bronchoscope, the condition clears up, only to recur with another obstructive episode; hence the recurrent pneumonic attacks.

When the obstruction becomes permanent, the segment of the lung distal to it becomes atelectatic and infected with pyogens, inducing pneumonitis, bronchiectasis, abscess and empyema.

Bronchostenosis and bronchial obstruction have been recognized for the past ten to fifteen years. Older clinicians (as well as pathologists), unaware of this phenomenon, focused attention on the parenchyma of the lung, which they treated without effect. Patients usually succumbed to complications. Indeed, early recognition of the source of the trouble followed by proper therapy is life saving.

That the adenoma has a tendency to affect larger bronchi (accessible to the bronchoscope) was mentioned in the introductory paragraphs. From a series of collected cases it would appear that it is encountered oftener on the right side. Of 217 cases from the literature, it occurred on the right side in 127, or 58.5 per cent, and on the left in 90, or 41.5 per cent. The lower lobe seems to be affected oftener than the upper.

The highest incidence of the disease is observed in the third and fourth decades, but persons in other age periods are not immune. According to Foster-Carter,[9] the majority of adenomas are recognized in patients between the ages of 30 and 40. Kramer and Som [10] observed an adenoma in a boy of 13, but 61 per cent of their patients were between the ages of 21 and 38. Jones and his associates [19] reported a case of an adenoma of the right main bronchus in a boy of 10 years. The boy died during a bronchoscopic examination. Of 123 cases culled from the available literature, 109 affected persons were under 50, and only 14 were above that age. It may be observed that bronchiogenic adenoma is but rarely seen at the age period when bronchiogenic carcinoma occurs most frequently.

Of interest, too, in this connection is the sex incidence. Of 160 cases, 71, or 44.25 per cent, occurred in men, and 89, or 55.75 per cent, occurred in women. These figures are of particular significance when compared with those found in cases of bronchiogenic carcinoma—80 per cent in men and only 20 per cent in women.

Bronchoscopy.—In the introductory paragraphs it was stated that the tumor has the aspect of a pouch constricted in the middle in an hourglass fashion; at the point of constriction it is astride on the bronchial wall, one segment advancing toward the lung and the other toward the bronchial lumen. The adenoma was also likened to an iceberg, one portion of which (endobronchial) is on the surface while the other (intrapulmonary) is submerged. It is thus apparent that, while the bronchoscopist is not in a position to ascertain the extent of the lesion, he is able to point out the diagnosis and remove tissue for microscopic study. The bronchoscopist is also in a position to remove the mucous

19. Jones, R.; Mackenzie, K. W., and Biddle, E.: Brit. J. Tuberc. **37**:113, 1943.

plug occluding the bronchial lumen, thus facilitating reaeration of the atelectatic portion of the lung before infection has set in.

Roentgenography.—Modern methods of bronchography with the use of an opaque substance reveal the location of the intrabronchial growth. By the use of tomography the intrapulmonary tumor is visualized as a round, dense shadow with well defined borders characteristic of benign tumors.

TREATMENT

With the advent of the recent concept of bronchiogenic adenoma, notions of its treatment have undergone changes. One no longer considers the treatment of the visible portion of the tumor with radium, forceps, electrocoagulation or aspiration alone sufficient to eradicate the disease. Two illustrative cases are incorporated in this report. The patient in case 2 received fourteen bronchoscopic treatments during a period of seven years, without result. She ultimately underwent a lobectomy, with the removal of a sizable intrapulmonary tumor (fig. 2). The patient in case 3 is still under observation but it is feared that she too will meet the same fate.

That some tumors are confined uniquely to the bronchial lumen has been demonstrated by Jackson, and case 1 in the present series is illustrative in this respect (fig. 1). Such tumors disappear under local treatment.

Lobectomy or pneumonectomy is resorted to in instances when the size and sessile attachment of the adenoma render its bronchoscopic removal impossible and also when putrid infection has set in. Those who state that bronchiogenic adenoma is potentially malignant and that most of them ultimately become cancerous advise removal of the lobe or of the entire lung the moment one arrives at the diagnosis.

REPORT OF CASES

CASE 2.—*History.*—A woman of 39 years was admitted to the hospital in 1937, complaining of pain at the bases of both lungs. Her past, family and marital histories were noncontributory. She had been well until 1933, when she contracted a severe "cold" accompanied with a stubborn cough. During a coughing spell she expectorated about a glassful of bright red blood, and a few days later another hemoptysis occurred, amounting to about 2 glassfuls.

Roentgenographic examination showed moderate cylindric dilatation of the bronchi at the bases. The sputum was negative for tubercle bacilli. She was discharged from the hospital after several weeks, with the diagnosis of pulmonary tuberculosis.

Although her cough abated, expectoration of blood persisted. On fluoroscopic examination a "shadow at the base of the left lung" was noticed. Pain in the lower part of the chest persisted as well as the sporadic hemoptyses, which at times amounted to half a cupful. She lost some weight. After a profuse hemoptysis, she was admitted to the Montefiore Hospital.

Bronchoscopy performed in May 1937 disclosed a readily bleeding purplish mass on the posterolateral branch of the bronchus of the lower lobe of the right lung.

Roentgenologic examination revealed within the pulmonary parenchyma a pear-shaped mass about 5 cm. in diameter; it was situated on the right side, external to the cardiac shadow. A roentgenographic examination performed seven months later, following the injection of iodized poppy seed oil, showed that the oil penetrated with difficulty into some branch bronchi of the lower lobe in the neighborhood of the mass. One branch bronchus in the vicinity was completely obstructed, and the lung around it showed no aeration.

The diagnosis was adenoma of the bronchus of the lower lobe of the right lung. The patient was treated by diathermy coagulation through the bronchoscope.

Interval Course.—She was discharged from the hospital improved, but soon small hemoptyses recurred. At times blood kept oozing for hours. While bronchoscopically the bronchial lumen was virtually patent, roentgenologically the tumor within the pulmonary parenchyma showed steady growth. From 1937 to 1944 the patient was admitted to the hospital fourteen times, receiving treatment through the bronchoscope. Hemoptyses could not be controlled. In 1944 it was finally decided to perform a lobectomy.

Lobectomy.—At operation the pleura overlying the tumor showed no inflammatory changes; the pleural cavity was patent, and most of the lung was crepitant and of normal color. A solitary tumor, lobulated, soft and encapsulated, measuring 6.5 by 5.0 by 4.5 cm., was found in the center of the lobe (fig. 2*A*). About 0.5 centimeter from the mass the main lobar bronchus showed a defect filled with tumor, which apparently originated here. There was a moderate bronchial dilatation.

The tumor (fig. 2*B*) was made up of columns of uniform cells separated by extremely thin connective tissue. No mitoses were found. The stroma was vascular, and the blood vessels were often engorged with blood. In the vicinity of the growth, tumor cells were seen within the wall of a compressed bronchus, but no tumor was found elsewhere. A comparative study of the histologic nature of the tumor with that of the biopsy specimen removed eight years previously proved them to be identical.

Comment.—The case is characteristic in the onset of the disease with cough and bloody expectoration and in its protracted course. Although the sputum was invariably negative for tubercle bacilli, the diagnosis of tuberculosis was entertained until the bronchoscopic examination revealed the nature of the disease. As the tumor grew endobronchially and within the pulmonary parenchyma its bronchoscopic removal was not alone sufficient to cure the disease. However, it was important in keeping the bronchial lumen patent, thus preventing atelectasis and putrid infection of the lung. About twelve years after the onset of symptoms lobectomy was resorted to, resulting in a cure.

The patient was readmitted to the hospital two years later for carcinoma of the breast. It would appear then that, although she had lurking possibilities for carcinogenesis, neither time nor repeated trauma had led to the transformation of the benign adenoma into a malignant carcinoma.

CASE 3.—*History.*—A single woman, a clerk aged 27, dated her illness back to February 1940, when she became aware of pain in the chest, cough, night sweats

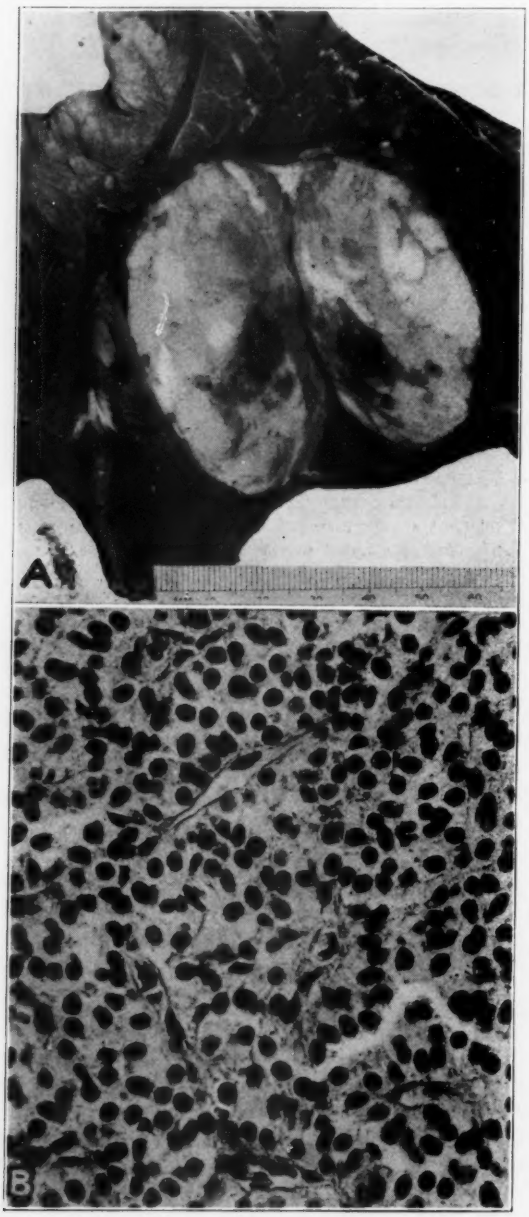

Fig. 2 (case 2).—*A*, cut surface of the adenoma removed at operation. *B*, histologic structure of the tumor.

and loss of weight and the fact that her sputum was blood streaked on several occasions. The diagnosis of pulmonary tuberculosis was made; she was given rest in bed, which led to her improvement until February 1941, when small hemoptyses recurred. The diagnosis of tuberculosis was reaffirmed, and a futile attempt to induce pneumothorax was made. She was again ordered to bed and remained bedridden until September, when she was transferred to a sanatorium for tuberculous patients. Her sputum remained free from tubercle bacilli. For several months she had perceived a wheezing sound in her chest.

On admission to the Montefiore Hospital she appeared to be well nourished. Loud sonorous rales were heard throughout the chest. The vital capacity was 2,600 and the sedimentation rate 40.

Roentgenologic examination revealed a wedge-shaped shadow, with its base at the mediastinum; it extended from the right hilus toward the periphery at the

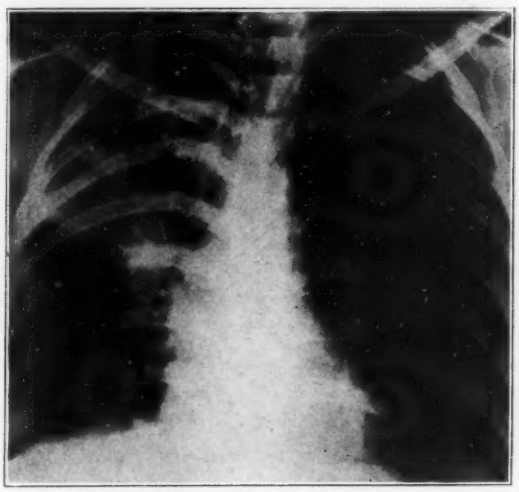

Fig. 3 (case 3).—Roentgenogram of the lungs, showing a triangular shadow on the right side due to atelectasis caused by obstruction of the bronchus.

level of the third rib anteriorly (fig. 3). There was some shrinkage of the upper lobe of the right lung; the trachea was retracted to the right side, and the right lung showed reduced expansion. The homolateral leaf of the diaphragm was elevated. The findings were indicative of lobar atelectasis due to stenosis of the bronchus of the upper lobe. The impression was that one was dealing with moderately advanced pulmonary tuberculosis accompanied with tuberculous endobronchitis.

On bronchoscopic examination the right bronchus was occluded by a smooth mass, which apparently originated in the posterior wall of the upper lobe of the right lung. A biopsy specimen was removed, which on histologic examination showed the tumor to be an exact replica of that in case 2.

Comment.—While in case 2 the disease had been observed in the preobstructive phase, in this case obstruction was quasicomplete when

the patient came under observation. She had as yet escaped the sequel of bronchostenosis, such as putrid infection of the lung or empyema. She is being treated bronchoscopically, but it is feared that eventually a

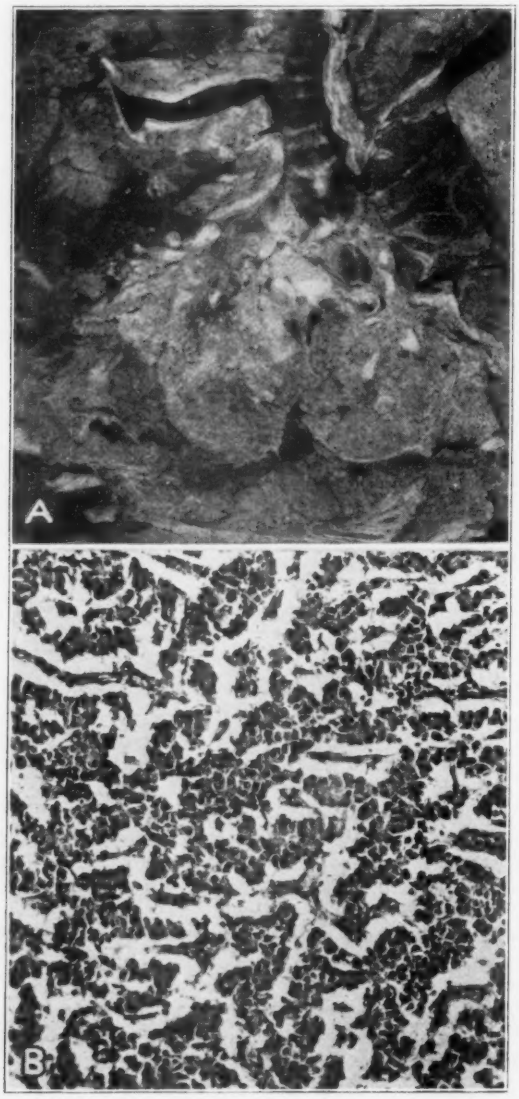

Fig. 4 (case 4).—*A*, cut surface of the adenoma surrounded by a capsule. *B*, histologic structure of the tumor.

lobectomy or pneumonectomy will have to be performed. Unlike the patient in case 2, in which the diagnosis of tuberculosis was entertained for a short time only, this patient was treated for tuberculosis for nearly two years.

CASE 4.—*History.*—Examination of a woman of 68 years revealed a dense shadow at the base of her right lung, diagnosed as bronchogenic carcinoma. Six years previously she had noticed blood-streaked sputum and occasional hemoptysis, and they had persisted for a few years. Reexamination two years later revealed the shadow unchanged, and as it moved with respiration it was interpreted as a benign tumor or possibly an organized abscess of the lung. Two years later she died of a cardiac condition.

At autopsy the lower lobe of the right lung was shrunken and distorted, and the pleura along the inferior border was thickened and deeply retracted. A firm mass was felt posteriorly in the region of the lower and middle lobes (fig. 4 *A*), and the rest of the lung was noncrepitant. The mass (3.5 by 4.5 cm.) was lodged in the lower portion of the lung posteromedially. It arose from the main bronchus to the lower lobe, about 3 cm. from the carina, completely obliterating the bronchial lumen. The branches to the lower lobe were almost completely obliterated and replaced by tumor. Only fragments of cartilage remained in the bronchial wall in this region.

The tumor grew within the bronchial lumen and within the parenchyma of the lung. It was sharply demarcated, encapsulated and hard as stone. The larger bronchial branches and the blood vessels in the vicinity of the tumor were merely pushed aside and compressed but not eroded or occluded. The bronchus to the middle lobe too was compressed but not obliterated, and the lobe was partially atelectatic. No metastases were present. The histologic nature of the tumor shown in figure 4 *B* is that of a solid adenoma of the bronchus. It is benign by all criteria.

Comment.—If one is to rely on the patient's story, except for hemoptyses and blood-streaked sputum she experienced no other ill effects from the neoplasm.

CASE 5.—*History.*—A pharmacist of 65 years was seen for the first time in June 1944 for pain in the dorsal part of the spine. His past history was irrelevant, and the physical examination revealed nothing worthy of note. On roentgenologic examination the spine showed no abnormalities, but a well circumscribed mass measuring about 6 cm. in diameter was noticed in the upper lobe of the right lung (fig. 5). The diagnosis of bronchiogenic carcinoma was made, and the patient was subjected to radiation therapy. While under treatment a pulmonary infection developed, to which he succumbed.

At necropsy a tumor 6 cm. in diameter was found in the upper lobe of the right lung posteriorly. It surrounded a secondary branch of the bronchus of the upper lobe without, however, narrowing the bronchial lumen. The bronchial wall was normal for about 3 cm., after which it abruptly closed, the bronchus being buried within the mass which enveloped it. The lungs showed considerable fibrosis. The tracheobronchial lymph nodes contained no tumor.

On microscopic examination the tumor was partitioned into lobules resembling those of the pancreas or the salivary gland. The cells were wholly degenerated, but their structure could be identified as polygonal or roughly round with round

nuclei. The new growth was surrounded by a capsule, the outer coat of which showed lamellary hyalinization, while the inner coat was densely hyalinized. Beyond the hyalin there was a ring of young fibrous tissue, possibly the reaction to the 7,000 r delivered to the patient's chest. No tumor was found elsewhere.

Comment.—Here is an instance of a wholly asymptomatic adenoma. The bronchial occlusion led to no known pulmonary complications. Apparently the tumor grew slowly, and with its capsule hyalinized it was entirely shut off from the circulation and became degenerated.

CASE 6.—*History.*—A married woman, aged 64, was in good health until she was 48 years, when diabetes, hypertension and hypertensive cardiovascular disease

Fig. 5 (case 5).—Roentgenogram showing bronchiogenic adenoma in the upper lobe of the right lung.

developed. On routine examination of her chest a round, sharply circumscribed area of density, 2 cm. in diameter, was noticed in the middle zone of the right lung anteriorly. The suggestion was made that it might be a metastasis, a tuberculous infiltration, an infarct or a bronchiogenic carcinoma (fig. 6 *B*).

At necropsy an encapsulated tumor measuring 2 cm. in diameter was found at the base of the upper lobe of the right lung (fig. 6 *A*). It arose in the mucosa of a small bronchus to the upper lobe. No metastases were found in the lymph nodes or in the viscera.

Comment.—In this case the adenoma was accidentally discovered during a roentgenologic examination. If in the past the tumor had caused disturbances they were apparently so mild as to be disregarded by the patient.

CONCLUDING NOTE

Unlike bronchiogenic carcinoma, adenoma of the bronchus represents a relatively simple diagnostic problem. Of paramount importance is the assertion that the tumor is potentially malignant and that in most

Fig. 6 (case 6).—*A*, cut surface of the lung, showing the circumscribed adenoma (arrow). *B*, roentgenogram showing the tumor in the right lung (arrow).

instances it "degenerates" into a bronchiogenic carcinoma. By some continental observers it has been defined as carcinoid and by others as basal cell carcinoma. It also has been stated that, while clinically it is benign, pathologically it is malignant (or semimalignant).

The view, however, that the adenoma is a benign tumor by nearly all criteria is gaining ground. Metastases have been observed in extremely few instances. They were few and minute and were discovered accidentally at the postmortem examination. No recurrences were observed following removal of the tumor which per se caused no deaths.

Not even locally (as some would have physicians believe) is the adenoma malignant. In its growth it may form a "bulge" but hardly ever a "break through." Indeed, the main characteristic of carcinoma, "schwerpunkt und aufrollen (break though and unfold)," is lacking in this tumor, which is surrounded by a capsule. The assertion that bronchiogenic adenoma often "degenerates" into bronchiogenic carcinoma has not been confirmed. The adenoma is, indeed, expansive but not invasive.

It is the commonest benign bronchial tumor, comprising from 6 to 12 per cent of all bronchial neoplasms. It is prevalent in patients in the third and fourth decades and occurs oftener in women and more frequently on the right side. It occurs in bronchi accessible to inspection with the bronchoscope and presumably easily diagnosed.

Therapy applied in the early stages eradicates the disease, while dilatoriness is fraught with dangerous complications, such as putrid abscess and bronchiectasis, pneumonitis and empyema.

PRIMARY HYPERTROPHY AND HYPERPLASIA OF THE PARATHYROID GLANDS ASSOCIATED WITH DUODENAL ULCER

Report of an Additional Case, with Special Reference to Metabolic, Gastrointestinal and Vascular Manifestations

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IN A PREVIOUS publication,[1] attention was called to the association of duodenal ulcer in 1 case with parathyroid adenoma and in a second case with primary hyperplasia of the parathyroid glands. In both cases the ingestion of large quantities of calcium and phosphorus in diets prescribed for the treatment of duodenal ulcer was associated with acute manifestations of hyperparathyroidism which terminated fatally. Since this report, a third case of probable hyperparathyroidism associated with duodenal ulcer has been observed. Primary hypertrophy and hyperplasia of the parathyroid glands were present in association with a well healed duodenal ulcer. In view of the diagnostic importance of gastrointestinal symptoms in hyperparathyroidism and because the coexistence of duodenal ulcer both obscures the diagnosis of hyperparathyroidism and complicates its treatment, this association deserves further emphasis. Furthermore, since primary hypertrophy of the parathyroid glands is uncommon, the finding of an additional case is noteworthy.

REPORT OF A CASE

The patient was a white man, aged 68 years, who was first seen at the Mayo Clinic in 1919, when posterior gastroenterostomy was performed because of duodenal ulcer. For many years thereafter he was reasonably well, but episodes of mild gastric distress continued to occur from time to time, most frequently in the spring or fall. He again registered at the clinic, on March 12, 1945, complaining of epigastric pain of four months' duration. Ingestion of food had been decreasingly effective in relieving the pain, and he stated that milk disagreed

Dr. Keating, Dr. Morlock and Dr. Barker are from the Division of Medicine, Mayo Clinic.

1. Rogers, H. M.: Parathyroid Adenoma and Hypertrophy of the Parathyroid Glands, J. A. M. A. **130**:22-28 (Jan. 5) 1946.

with him. Anorexia and nausea had been present for six weeks; vomiting had occurred two weeks previously, and during the previous week it had occurred eight times, usually giving relief from nausea. No special diet had been observed. Constipation accompanied the appearance of epigastric pain. The patient had lost 25 pounds (11.3 Kg.).

In addition to the foregoing complaints, the patient had experienced certain symptoms referable to the skeletal system. For two to three years he had felt

Fig. 1.—Posterior view of the organs of the neck, demonstrating primary hypertrophy of the parathyroid glands. The esophagus has been opened. The left superior and right superior parathyroid glands are seen as well as the superior portions of both lobes of the thyroid.

pain in the right foot, occurring when he was walking or bearing weight. This pain extended from the right heel to the right hip, and there was occasionally pain in the left hip. For two years pain had been present in the ankles, knees and shoulders, and the patient had noticed stiffness and weakness. His family noticed that he appeared bent over when walking.

Physical examination revealed a tall, thin, elderly man. The pulse rate was 70 beats per minute. The blood pressure ranged from 130 to 140 mm. of mercury systolic and from 92 to 100 diastolic. A systolic aortic murmur was heard. All palpable vessels were much thickened, and radial sclerosis was pronounced. There was muscular atrophy, with wasting and weakness of all muscles of the arms and legs. The thoracic portion of the spinal column was moderately kyphotic. The prostate was moderately enlarged on palpation.

The examination of the urine revealed a specific gravity of 1.012, an acid reaction and the presence of albumin (grade 2; on the basis of 1 to 4, in which

Fig. 2.—Primary hypertrophy of the parathyroid glands. Illustrated are the left superior, middle and inferior parathyroid glands and the right superior, middle and inferior parathyroid glands. Pseudopodal projections are seen from the left and right superior glands.

1 designates the mildest and 4 the severest condition). No sugar was found, and microscopic studies of sediment gave normal results. The concentration of hemoglobin was 13.1 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 4,140,000 and leukocytes 10,000 in each cubic millimeter of blood. The routine flocculation test for syphilis gave negative results. Roentgenograms revealed scoliosis and kyphosis in the upper part of the thoracic area, an old duodenal ulcer and a diverticulum of the second portion of the duodenum.

The patient was hospitalized, and a modified diet for patients with ulcer was prescribed, which contained 1.7 Gm. of calcium and 1.4 Gm. of phosphorus augmented daily with aluminum phosphate gel. Despite treatment, moderate epigastric distress was still present at the time of his dismissal on March 28, 1945. While a gastrojejunal ulcer was suspected, it was observed that the typical shift of pain to the left had not occurred.

At the time of the patient's next examination, on Oct. 1, 1945, he complained mainly of blueness of the great toe of the left foot, of one week's duration. Generalized pruritus, nervousness and insomnia had been present for four weeks. In the interim between examinations vomiting three to four times weekly had occurred from June to September, and pronounced polydipsia and polyuria had been present during this time. Increasing pain in the right leg and weakness had been present for two weeks. Mental confusion began one to two weeks preceding this admission.

The results of physical examination were the same, except for gangrene of the great toe of the left foot. Dorsalis pedis and posterior tibial arterial pulsations were absent bilaterally, while popliteal and femoral arterial pulsations were normal bilaterally.

Dimensions and Weights of Parathyroid Glands

	Dimensions, Cm.	Weight, Gm.
Right superior parathyroid	5.2 by 2.2 by 2.0	14.2
Right middle parathyroid	1.2 by 0.5 by 0.5	0.55
Right inferior parathyroid	1.8 by 0.6 by 0.3	0.36
Left superior parathyroid	7.2 by 4.5 by 2.8	30.9
Left middle parathyroid	2.2 by 1.0 by 0.9	1.45
Left inferior parathyroid	1.2 by 0.5 by 0.2	0.1
		47.56

The results of studies of the urine were unchanged. The concentration of hemoglobin was 7.5 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 2,350,000 and leukocytes 15,600 in each cubic millimeter of blood. A roentgenologic examination of the thorax revealed prominence of the left ventricle. An electrocardiogram was normal except for premature auricular contractions. The concentration of urea was 182 mg., and that of cholesterol was 107 mg. per hundred cubic centimeters of blood. The fatty acids were 261 mg. and the total lipids were 368 mg. per hundred cubic centimeters of plasma.

Intravenous administration of dextrose was instituted, but progressive disorientation occurred, and on October 4, three days after his admission to the hospital, the patient became comatose. The concentration of urea rose to 258 mg. per hundred cubic centimeters of blood. Death occurred on October 5, four days after his final admission.

Observations at Necropsy.—At postmortem examination the following observations were deemed significant. There was definite hypertrophy of the parathyroid glands and supernumerary glands (figs. 1 and 2). The weights and measurements of the individual parathyroid glands are given in the table. The parathyroid glands were firm and brown. Pseudopodal projections were observed from the right superior parathyroid gland measuring 1.5 by 0.5 by 0.3 cm. and 1.0 by 1.0 by 0.4 cm. and from the left superior parathyroid measuring 2.7 by 1.7 by 1.0 cm. and 1.0 by 1.0 by 0.8 cm. Cysts were present in the left superior parathyroid gland, and small petechial hemorrhages were present over their

surfaces. The cut surface of this gland (fig. 3) revealed one large cystic area, measuring 2.0 by 2.2 by 1.8 cm., in the midportion of the gland, composed of smaller cystlike cavities, measuring 1 to 2 mm. in diameter and filled with blood. Small hemorrhagic cysts, measuring 0.3 and 0.5 cm. in diameter, were also present in the left superior parathyroid gland, and two cysts containing clear fluid and measuring 0.5 cm. and 0.2 cm. were present in the right superior parathyroid gland. The total mass of parathyroid tissue weighed 47.56 Gm.

The lungs revealed purulent bronchitis, grade 1. The heart was hypertrophic and weighed 506 Gm.

In the stomach there was an old posterior gastroenterostomy scar, the stoma of which measured 0.4 cm. in diameter. There were a healed jejunal ulcer and a healed duodenal ulcer. Diverticula were present in the duodenum and the sigmoid colon. The pancreas weighed 90 Gm. Throughout the pancreas there were multiple mulberry-shaped deposits of calcium which ranged in diameter from 0.4 cm. up to 2.0 cm. There was moderate dilatation of the pancreatic ducts.

Fig. 3.—The left superior and right superior parathyroid glands. One large and two small cysts with hemorrhage are present in the left superior gland.

The right kidney weighed 113 Gm. and the left kidney 145 Gm. Their surfaces were diffusely granular and contained parenchymatous cysts ranging from 0.5 to 3.8 cm. in diameter. The cut surfaces were brown, with small white regions in the medullae, measuring up to 1 mm. in diameter.

There was dry gangrene of the great toe of the left foot.

The histologic appearance of all the parathyroid glands was similar except for minor variations. The constant type of cell throughout was the large water-clear cell (fig. 4). The diameter of these cells varied from 8 to 38 microns, the large majority of the cells being from 18 to 22 microns. In most of the cells the nucleus was small, but in a few instances larger nuclei were observed. There was characteristic polarity of the nucleus, which frequently was located at the periphery of the cell. Mitotic figures were absent. The cytoplasm was clear except for a few eosinophilic granules in the periphery of some cells. Small deposits of glycogen were present in the cytoplasm of some of the cells. Mucin stains gave negative results, and frozen sections stained with sudan II did not disclose fat. In some sections the cells were arranged in solid sheets, but in most regions there was a tendency toward acinar arrangement with pseudoglandular formation. Adipose connective tissue cells were absent, and connective tissue stroma was for

the most part sparse. Blood vessels were numerous. Hemorrhage was present in some of the cystic regions observed in the left superior parathyroid gland. The microscopic appearance was typical of that described previously in cases of primary hypertrophy and hyperplasia of the parathyroid glands.

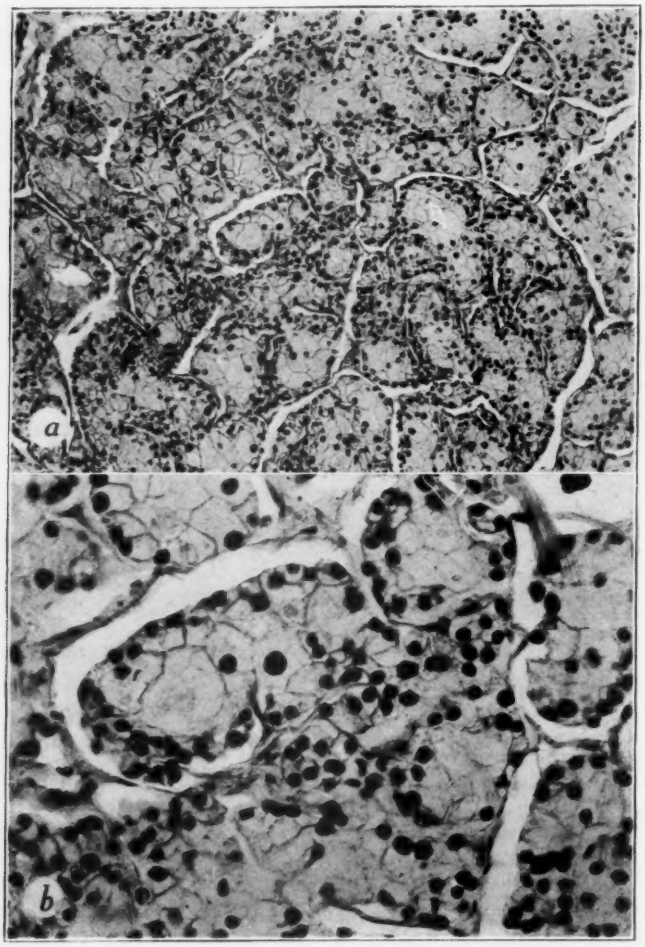

Fig. 4.—Parathyroid gland. *a*, typical appearance of primary hyperplasia, showing acinar grouping. In some regions the cells assumed the form of solid columns. × 120. *b*, higher magnification, showing the large *wasserhelle* cells with clear cytoplasm. Note polarity of the nuclei. × 350.

All sections of the thyroid gland were normal. The sections of the lungs were normal, but in the larger bronchi polymorphonuclear leukocytes were present.

In all sections of the pancreas there was decided dilatation of the ducts. Deposits of calcium were present within the ducts and throughout the parenchymal tissue. The acinar cells in the head of the pancreas were normal. In the tail of

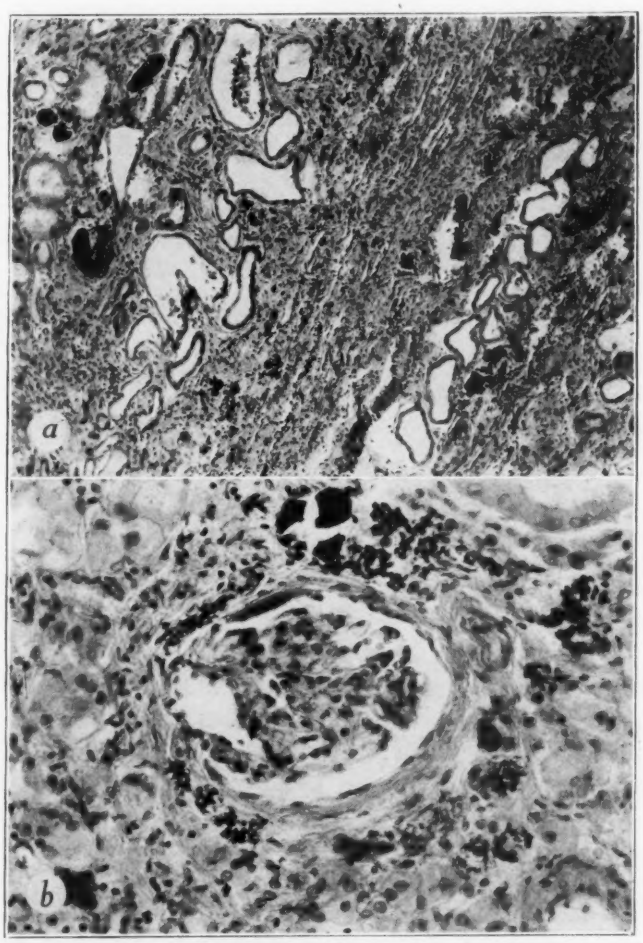

Fig. 5.—*a*, kidney, showing nephrocalcinosis. Deposits of calcium are present in the interstitial tissue. × 85. *b*, deposits of calcium in tubules surrounding a glomerulus. × 250.

the pancreas, atrophy of the glandular elements was striking, with replacement by fibrous connective tissue. The islets were preserved.

In the kidney two distinct changes were noted. Most striking of these was widespread nephrocalcinosis (fig. 5). Deposits of calcium were observed in both

convoluted and collecting tubules, and in some instances these were associated with necrosis of the epithelial cells. Interstitial deposits of calcium were likewise present. In addition there was atrophy, as seen in arteriosclerotic kidneys. These

Fig. 6.—Section of a vertebra, showing fibrous change suggestive of osteitis fibrosa cystica. × 115.

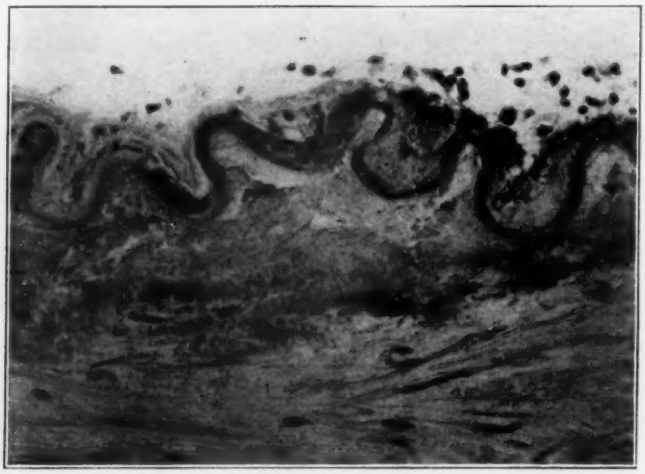

Fig. 7.—Branch of a renal artery, illustrating deposits of calcium in the internal elastic lamina. × 300.

changes consisted of medial thickening of many small and medium-sized arteries, an occasional hyalinized glomerulus, atrophic tubules in some regions with dilated

tubules in others, swollen tubular epithelial cells and increase of interstitial tissue with lymphocytes.

In decalcified sections of the vertebrae (fig. 6) and ribs there was well marked osteitis fibrosa with small cysts. Osteoclasts were present in greatly increased numbers at the edges of the trabeculae of the bone.

Examinations of sections of the larger arteries (the aorta, renal, superior mesenteric, common and external iliac, right popliteal and coronary arteries) showed a moderate degree of patchy atheromatous degeneration and scattered small deposits of calcium in the medial coats. These changes were not remarkable or excessive for the patient's age. However, an unusual type of arterial lesion was seen in almost all the sections studied. This consisted, in every section, of one or more irregular patches of necrosis of the arterial wall, which were sometimes of considerable size. In these patches the cells of the muscular and fibrous tissue had lost their nuclei but retained their form and arrangement. Around the irregular margin of the necrotic patch was a fine, darkly stained line of calcium deposit. Otherwise, there was little or no calcium in the necrotic tissue. In some regions the necrotic patch involved the intima, and here the irregular boundary of calcium was seen in the internal elastic lamina (fig. 7).

Fig. 8.—Postmortem roentgenogram of the pancreas, showing multiple pancreatic calculi.

A review of the roentgenograms of the spinal column revealed mild demineralization, with coarsening and widening of the trabeculations of the vertebrae, consistent with hyperparathyroidism. Postmortem roentgenologic study of the kidneys disclosed diffuse calcification of the parenchyma and calcification of the main renal arteries and their smaller branches. A portion of each kidney was analyzed for calcium; the right kidney contained 3.43 mg. of calcium per gram of wet tissue and 16.74 mg. per gram of dry tissue; the left kidney contained 1.86 mg. of calcium per gram of wet tissue and 9.19 mg. of calcium per gram of dry tissue. A roentgenogram of the pancreas taken after death revealed extreme calcification (fig. 8). On analysis, one of the pancreatic calculi was found to contain only calcium carbonate.

COMMENT

Pathologic Considerations.—The parathyroid glands in this case demonstrated the typical appearance of "primary hypertrophy" of the parathyroids with characteristic pseudopodia. There were supernumerary parathyroids, and the possibility that they originated as pseudopodia from the main glands must be entertained. Cysts and hemorrhage were observed in the larger glands. Histologically, the large clear cell was

constant in all glands. The weight of the parathyroid tissue (47.56 Gm.) is the greatest recorded in instances of primary hypertrophy and hyperplasia.

Primary hypertrophy or hyperplasia of the parathyroid glands, as illustrated by this case, must not be confused with secondary hyperplasia of the parathyroid glands occurring in cases of long-standing renal insufficiency.[2] In cases of secondary hyperplasia, enlargement does not reach the degree observed in this case, and histologically the gland is composed of chief cells, alone or in combination with oxyphil cells. In primary hyperplasia the histologic examination discloses only large water-clear (*wasserhelle*) cells.

Primary hyperplasia has been observed infrequently. In the large series of cases of primary hyperparathyroidism observed at the Massachusetts General Hospital by Albright [3] and Cope [4] and their colleagues, it has occurred eight times. Albright has suggested that the process represents hypertrophy rather than hyperplasia, because in his material he found that the mean size of the cell was increased sufficiently to account for the increased mass of the glands without assuming any increase in the number of cells. However, in this case, as in the case of primary hyperplasia previously reported from the Mayo Clinic, the increased size of the cell appears totally inadequate to account for the weight of the glands. In the present instance the weight, 47.56 Gm., represents an increase of approximately four hundred times over the normal weight of the parathyroids. We, therefore, feel that "hyperplasia" is a more accurate designation for this process than "hypertrophy."

The lesions in the larger arteries are worthy of some comment. The peculiar regions of necrosis surrounded by a fine boundary of calcium had the appearance of infarcts of the arterial wall, and all appeared to be of approximately the same age. It is uncertain whether the hypercalcemia produced these lesions or whether the calcium was merely being deposited in a region of degenerated tissue, as so often occurs in patients without parathyroid disease. Inasmuch as the lesions involved the intima and internal elastic lamina in some instances, it is obvious that they might be favorable sites for the development of thrombosis. This

2. Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. **13**:553-574 (July) 1937; The Pathology of the Parathyroid Gland in Hyperparathyroidism: A Study of Twenty-Five Cases, ibid. **11**:1-72 (Jan.) 1935.

3. Albright, F.: The Parathyroids: Physiology and Therapeutics, J. A. M. A. **117**:527-533 (Aug. 16) 1941.

4. Cope, O.: Hyperparathyroidism: Sixty-seven Cases in Ten Years, J. Missouri M. A. **39**:273-278 (Sept.) 1942; Hyperparathyroidism: The Significance of Generalized Hyperplasia; Report of the Seventh Case, Clinics **1**:1168-1178 (Feb.) 1943.

is the probable explanation for the occlusion of the arteries of the legs and the gangrene of the great toe of the left foot. These arterial lesions represent a somewhat different mechanism from the usual type of arteriosclerosis obliterans which is seen in elderly persons who have extensive atheroma.

The Diagnosis of Hyperparathyroidism.—The possibility that this patient had hyperparathyroidism was not considered during life. Since the blood and urine were not analyzed for calcium or phosphorus, chemical confirmation of this diagnosis was not obtained. When the record is reviewed in the light of the postmortem observations, however, the existence of primary hyperparathyroidism may be assumed with considerable assurance. So far as is known, hyperplasia of the parathyroids involving *wasserhelle* cells is always associated with primary hyperparathyroidism. The finding at necropsy of nephrocalcinosis and changes in the bones characteristic of osteitis fibrosa cystica further confirms this diagnosis.

In retrospect, a good many of the symptoms presented by the patient could be ascribed to hyperparathyroidism. The history of skeletal pain for three years suggested osseous involvement, and the roentgenograms showed mild but definite changes which were compatible with hyperparathyroidism but not pathognomonic of it. Epigastric pain, constipation, anorexia, vomiting and loss of weight, which were present during the last year of life, probably resulted from hypercalcemia; the weakness and mental confusion may have had the same significance. The polyuria and polydipsia, as well as the terminal azotemia, are consistent with the renal manifestations of hyperparathyroidism.

The clinical diagnosis of hyperparathyroidism depends on the demonstration of an increased concentration of calcium and a reduced concentration of phosphorus in the serum together with an increased excretion of calcium in the urine, although these abnormalities may be obscured or effaced in the presence of severe and protracted renal insufficiency. The clinician is usually induced to seek chemical proof of abnormal function of the parathyroids only when his suspicion is aroused by some spectacular manifestation of hyperparathyroidism. For many years the diagnosis was made only in cases in which the far advanced manifestations of skeletal demineralization known as von Recklinghausen's osteitis fibrosa cystica were present. In more recent years, as a result of the studies of Albright and his colleagues,[5] suspicion of hyperparathyroidism has been aroused by the occurrence of renal stones.

5. Albright, F.; Aub, J. C., and Bauer, W.: Hyperparathyroidism: A Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, J. A. M. A. **102**:1276-1287 (April 21) 1934. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: IV. Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**:49-65 (Jan.) 1934.

It is becoming apparent, however, that hyperparathyroidism may exist, perhaps for a long time, without producing either conspicuous skeletal symptoms or renal stones. Albright [6] has reported 1 case in which hyperparathyroidism was suspected because of pronounced weakness and lassitude. Careful examination disclosed minimal demineralization of the skeleton, but chemical criteria of hyperparathyroidism were found and an adenoma was removed at operation. One of us [7] has observed a case in which hypercalcemia and hypophosphatemia were found more or less by accident. In this case careful observation over a period of two years failed to disclose any symptoms which could be referred to hyperparathyroidism; yet exploration disclosed a parathyroid tumor. It is evident, therefore, that hyperparathyroidism may occur without conspicuous osseous disease and without renal calculi. In the case being reported, the roentgenographic changes in the skeleton were minimal and not in themselves pathognomonic of hyperparathyroidism, although they become highly significant when viewed in the light of the postmortem observations.

When hyperparathyroidism occurs without either skeletal or renal involvement, the only symptoms that one might expect to encounter would be those resulting from hypercalcemia per se or from the resulting hypercalciuria. These include nausea, vomiting, anorexia, loss of weight, epigastric pain, weakness, constipation, polyuria and polydipsia. Hypervitaminosis D results in hypercalcemia and may also produce such symptoms. Hypervitaminosis D may also result in renal insufficiency or the formation of renal stones. It must, therefore, be carefully excluded before a diagnosis of hyperparathyroidism is made.

Renal Insufficiency.—Death in this case was probably the result of renal insufficiency secondary to hyperparathyroidism. The kidneys showed atrophy, in contrast to the 2 cases of hyperparathyroidism previously reported, in which hypertrophy of the kidneys was present. However, in this instance hyperparathyroidism may have existed for a longer period, and it is possible that the changes observed in these kidneys represent a later stage of the disease. Evidence of changes resulting from hyperparathyroidism is superimposed on the changes that are manifestations of vascular disease of the kidneys in this case. The calcium content of the kidneys was fifty to seventy-five times that found in normal kidneys.

Although the patient had evidence of considerable arterial disease of the kidneys, the degree of destruction of nephrons and replacement by fibrous tissue was out of all proportion to the degree of arterial

6. Albright, F.; Sulkowitch, H. W., and Bloomberg, E.: Further Experience in the Diagnosis of Hyperparathyroidism, Including a Discussion of Cases with a Minimal Degree of Hyperparathyroidism, Am. J. M. Sc. **193**:800-812 (June) 1937.

7. Keating, F. R., Jr.: Unpublished data.

disease. In our experience, death from renal insufficiency as the result of senile arteriosclerosis of the kidneys alone is rare. Also a significant degree of azotemia in an elderly patient can rarely be ascribed to senile renal arteriosclerosis alone and without accompanying hypertension, chronic pyelonephritis or obstructive lesions of the urinary tract.

Gastrointestinal Features.—The gastrointestinal manifestations of hyperparathyroidism deserve further emphasis. Gutman and his associates [8] in 1934 described anorexia, nausea, vomiting, constipation and epigastric pain in cases of hyperparathyroidism and stated that these symptoms may so dominate the picture as to suggest that they are due to duodenal ulcer or appendicitis. It is a common fallacy to attribute symptoms of abdominal pain and vomiting first to some intra-abdominal disease and to assign a secondary etiologic role to a systemic disease which may chance to coexist. Because of this, it is not surprising that if an intra-abdominal lesion is found which could explain such symptoms the possibility that they result from an associated systemic disease is not seriously considered.

Vomiting is a common symptom of gastrointestinal disease. Peptic ulcer involving either the stomach or the duodenum is frequently accompanied with this symptom, but when vomiting is severe it is usually because the ulcer has been complicated by pyloric obstruction as a result either of spasm or of cicatricial change. In uncomplicated duodenal ulcer, involuntary vomiting, as distinguished from regurgitation and voluntary vomiting, is uncommon. Nervous and hysterical patients who have duodenal ulcer without any associated obstructive complication may have definite symptoms of nausea and vomiting. There are certain cases of duodenal ulcer in which there is no manifestation of the activity of the disease, except for severe unheralded and often protracted episodes of vomiting; this has been called the crisis type of duodenal ulcer.

If a patient who has duodenal ulcer has vomiting as a prominent symptom and it can be determined that the vomiting is not due to some complication of the duodenal ulcer or a functional manifestation, the explanation for the vomiting should be sought in some other disease process if adequate treatment of the ulcer fails to control the symptoms.

The lack of control of symptoms in this case was attributed to intractability on the part of the ulcer, and the possible significance of moderate aggravation of symptoms following treatment, considered adequate, was not recognized. When the history and course are reviewed in the light of the postmortem findings, they may be interpreted in a far different light than that which appeared most reasonable at the

8. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87-94 (July 14) 1934.

time of observation. On the basis of our retrospective knowledge that the duodenal ulcer was healed, it appears likely that the gastric symptoms which were present during the last eleven months of life were entirely manifestations of hyperparathyroidism. Treatment for the supposedly active ulcer not only failed to bring relief but can safely be presumed to have accelerated the injurious effect of the hyperparathyroidism on the kidneys and also, perhaps, on the blood vessels. The patient was probably correct in stating, as he did, that milk did not agree with him.

Albright has pointed out that demonstrable disease of bone does not develop in cases of hyperparathyroidism if a positive calcium balance is maintained. The fact that the usual diet taken by patients with ulcers is high in calcium and that this patient had symptoms of ulcer intermittently over a period of twenty-six years suggests that he probably maintained an intake of calcium higher than normal for many years. He should have been able to maintain calcium balance fairly well despite the association of hyperparathyroidism, but the finding of osteitis fibrosa cystica at necropsy shows that this was not the case.

Albright also suggested that if the serum calcium content is near the critical level a slight increase of it may precipitate symptoms of parathyroid poisoning and that a diet high in calcium or phosphorus may suffice to elevate the serum calcium content above the critical level. He emphasized that a patient who has severe hyperparathyroidism should be kept on a low intake of calcium and phosphorus until there is no longer any danger of parathyroid poisoning. Milk, which is the sheet anchor of the dietary for patients with ulcer, has, therefore, no place in the dietary program of the patient who has hyperparathyroidism. According to Sherman,[9] the average daily requirement of men is 0.68 Gm. of calcium and 1.32 Gm. of phosphorus. The average diet for patients with ulcer contains from 1.7 to 1.8 Gm. of calcium and from 1.3 to 1.4 Gm. of phosphorus daily. Such a high intake of calcium and phosphorus could probably precipitate acute parathyroid poisoning in cases of hyperparathyroidism. Such a sequence of events was apparently operative in 2 similar cases reported elsewhere by one of us (Rogers).

The fact that this case represents the third instance in which the association of probable hyperparathyroidism and peptic ulcer was observed at necropsy during one year at the Mayo Clinic suggests that this association may not be a chance one. There seems no compelling reason to suppose that hyperparathyroidism would favor the production of peptic ulcer, and chronologically it looks as if ulcer may

9. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 6, New York, The Macmillan Company, 1941.

have preceded parathyroid disease in this case. One may, therefore, wonder if treatment for ulcer over a long period may not have stimulated parathyroid hyperfunction as a result of the excess ingestion of alkalis, of calcium or of phosphorus.

The decided calcification of the pancreas is of considerable interest. Just what role the hyperparathyroidism played in the production of the pancreatic lithiasis is problematic. Although the pancreatic lithiasis may have been entirely secondary to recurrent pancreatitis, there was no past history for this, and it is possible that the tendency toward calcification elsewhere in the body, attributable to the hypercalcemia of hyperparathyroidism, may have played a part in the production of the pancreatic lithiasis. From the evidence at hand, one cannot say whether this is the case or whether the extensive pancreatic calcification was merely incidental.

SUMMARY

A case is reported in which pronounced clear cell hyperplasia of the parathyroid glands and primary hyperparathyroidism were associated with healed duodenal ulcer. The parathyroid glands weighed 47.56 Gm. Peripheral gangrene developed as a terminal event. Death resulted from renal insufficiency secondary to nephrocalcinosis. Pancreatic lithiasis and mild osteitis fibrosa cystica were also disclosed at necropsy. An unusual type of necrosis of arterial walls, with intimal calcification, appeared responsible for the gangrene of the peripheral parts. Gastrointestinal symptoms, which were presumed during life to be due entirely to ulcer, appeared in retrospect to have been manifestations of severe hyperparathyroidism.

COINCIDENCE OF DIABETES MELLITUS AND HYPOPITUITARISM

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THE INFLUENCE of the endocrine glands other than the pancreas on diabetes has been studied extensively. While the pancreas has always been the focus of research efforts, the modifying effects of other endocrine glands, notably the thyroid and adrenal glands, have also been considered of great importance. The research of Houssay and his associates [1] and of many other workers during the past fifteen years on the interrelationships of the pituitary, adrenal and pancreas is well known. The disease diabetes mellitus responds sensitively, either for better or for worse, to changes in the pituitary and adrenal. These changes may be artificially produced either by operation on the two glands or by injection of their hormones. The classic animal with the Houssay phenomenon is one in which diabetes has been produced by pancreatectomy and subsequently alleviated by hypophysectomy. An almost identical phenomenon can be produced by bilateral adrenalectomy only when the salt level is maintained.

The human equivalents of animals with the Houssay phenomenon are rare indeed. Reports of cases in which diabetes mellitus has been mitigated by the subsequent declining function of the adrenal or pituitary are exceptional. Some 16 cases of coincidence of diabetes and Addison's disease have been reported. Of these, only 4 apparently showed decreasing requirements for insulin as the hypoadrenalism developed.

The coincidence of diabetes mellitus and hypopituitarism is rarer still. We have found reports of only 3 patients displaying this phase of the Houssay phenomenon. In this paper we are reporting a fourth case.

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1. Houssay, B. A.; Foglia, V. G.; Smith, F. S.; Rielti, C. T., and Houssay, A. B.: The Hypothesis and Secretion of Insulin, J. Exper. Med. **75**:547-566, 1942.

REPORT OF A CASE

A 50 year old white married woman was admitted to Albany Hospital on July 2, 1943. Her chief complaints were headache, vomiting, dizziness, diarrhea and fainting spells.

The patient was in good health until thirty-one years ago. At that time she had a thyroidectomy, with apparent relief from the symptoms of hyperthyroidism. Subsequently she had an operation for the removal of fibroid tumors from the uterus and an operation on the breast the nature of which is not known.

Twelve years ago the patient's symptoms were diagnosed as diabetes mellitus, and she was treated in Detroit, where she received 50 units of insulin for ten days and then took 35 units of insulin a day for five to six months. From 1931 to 1934 she took 20 units of insulin a day sporadically but followed no strict regimen. For two or three years before her admission to the hospital she did not take any insulin at all. However, urinalyses often revealed sugar until about one year before admission, when the specimens of urine were consistently negative for sugar.

The patient was otherwise well until May 1, 1943, when she complained of a severe headache over her left eye. She became weak and started vomiting. For this she was hospitalized elsewhere for two weeks and then discharged as improved, without a diagnosis being made. One week after discharge, severe headaches returned and the patient's sense of smell seemed to be extremely acute. She was nauseated at the sight of food and would often vomit, sometimes without apparent cause. The vomitus was described as somewhat projectile in nature. When she stood, she became dizzy and weak. Her appetite became poor, and she began to lose weight. On several occasions when getting out of bed to go to the bathroom, she fell to the floor and lost consciousness temporarily. At these times, her hands assumed a clawlike position and she lost control of both her anal and her bladder sphincters. After these spells, the patient was weak and sweated excessively.

On June 1, 1943, the day before her admission to the hospital, the patient began to act rather silly for about two hours in the morning. She made faces at her husband, played peek-a-boo with the bed clothes and talked incoherently. After this, she appeared normal and slept. The next morning she was restless and thrashed her arms and legs about the bed. She talked only in a whisper and occasionally screamed in a loud voice. She was unable to retain food or fluids. Later in the day she began whispering and screaming and complained of a headache. She was brought to the hospital.

Family History.—One brother had diabetes, and the patient's mother died of diabetes. Her father died of carcinoma of the liver; the primary site was not known.

Past History.—The patient was married twenty-six years. She had always been pampered by her husband, who appeared to be a reliable and intelligent man. She reacted excessively to minor misfortunes, smoked excessively and drove an automobile extremely conservatively, i. e., 10 miles an hour.

Physical Examination.—The temperature was 99.2 F., the pulse rate 92, the respiratory rate 24 and the blood pressure 75 systolic and 30 diastolic. The abnormal findings were limited to the skin, which showed slight scleroderma, a thyroidectomy scar, a scar beneath the left breast and a laparotomy scar in the midline; the heart and lungs were essentially normal.

Neurologic Examination.—The left pupil was irregular and small but reacted to light. The right pupil was small and regular, reacting to light sluggishly.

There was variable spasticity of the arms and legs. Questionable deep reflexes were elicited from the left leg. The right leg and upper extremities showed normal reflexes. The abdominal reflexes were absent. The finger to nose test showed a 2 to 3 cm. deviation on the left.

Mental Status.—The patient's mood was one of flatness and indifference. She answered questions slowly and was able to give a chronologic account of her illness. She seemed oriented in all spheres when she was first seen.

Laboratory Data.—The urine showed a trace of albumin. The blood showed a hemoglobin content of 89 per cent; a red blood cell count of 4,900,000, with a color index of 0.96; a white blood cell count of 8,200, with a differential count of lymphocytes 73 per cent and polymorphonuclear leukocytes 27 per cent, and a hematocrit reading of 42 per cent. Wassermann tests of the blood and spinal fluid elicited negative reactions. The protein content was 44.2 mg. per hundred cubic centimeters, sugar content 35 mg., chloride contents 680 mg. and initial pressure 140 mm. of water. Roentgenograms, including a series of the gastrointestinal tract, were normal except for calcified mesenteric nodes. There was increased density of the left side of the pelvis, with no evidence of metastatic tumor in the lungs or in the ribs; the skull was normal. The basal metabolic rate was + 12 per cent. The blood sugar content was 61 mg. per hundred cubic centimeters. Gastric analysis showed 10 degrees of free hydrochloric acid.

Course in Hospital.—Because of the low initial blood pressure, this determination was repeated and showed, with the patient lying down, a pulse rate of 72 and a blood pressure of 75 systolic and 30 diastolic. With the patient sitting up, the pulse rate was not detectable and the blood pressure was 30 systolic and 0 diastolic. A tentative diagnosis of Addison's disease was made, and a determination of blood sodium content at this time showed the sodium content to be 327 mg. per hundred milliliters of serum. This was within normal range.

The patient became clear mentally and was in good contact. She became weak on sitting, somewhat faint and dizzy and required support. On July 15, 1943 she vomited twice and noted headache when she lay back. She was given isotonic solution of sodium chloride and dextrose intravenously and vitamins. She complained of pain in the knees; her knees on admission had been stiff and showed increasing lack of mobility as her stay in the hospital progressed. Her knees were painful on both active and passive motion. No pigmentation was noted. On a high sodium, low potassium diet, the patient showed no significant improvement. The provocative sodium withdrawal test was not attempted. Medical consultation was obtained, and the observations listed heretofore were corroborated. The suggestion was made that perhaps hypoactivity of the pituitary and thyroid might be indicated here. Studies of the blood pressure, which were made on the twenty-fifth day in the hospital, showed an initial blood pressure of 110 systolic and 60 diastolic with the patient horizontal and a drop to 72 systolic and 50 diastolic as the patient was gradually elevated. With the patient lying at an angle of 90 degrees, with the legs dependent, the blood pressure was 60 systolic and 40 diastolic. After an intramuscular injection of 0.5 cc. of epinephrine, with the patient at an angle of 90 degrees, with the legs dependent, there was no essential change in the blood pressure and she became nauseated. With the patient at an angle of 70 degrees and the legs elevated the blood pressure rose as high as 164 systolic and 82 diastolic, and with the patient lying flat the blood pressure was 130 systolic and 70 diastolic with the use of epinephrine.

On July 30, 1943, administration of adrenal cortical extract was started. Five cubic centimeters was given daily by intramuscular injection. On the first day

the blood pressure was 118 systolic and 66 diastolic with the patient reclining and 60 systolic and 44 diastolic with the patient sitting. On several occasions the blood pressure rose to 120 systolic and 70 diastolic, but there was no other essential change in the patient's condition. On Aug. 4, 1943 the patient became semicomatose, lashed around in bed, was unable to talk and vomited several times. Her muscles were spastic, and her hands were held in a clawlike position. Trousseau's sign was positive; there was no Chvostek's sign. Thereupon calcium gluconate was administered, with slight response. The patient was treated intravenously with a solution of dextrose in isotonic solution of sodium chloride, with some improvement, although she was not fully conscious all the time. Her speech was thick and she continued to vomit. On Aug. 6, 1943 the patient's blood pressure when reclining was 112 systolic and 65 diastolic, this being the seventh day of treatment with desoxycorticosterone acetate. She was fully conscious but was still weak and unable to retain food and was sustained on dextrose in isotonic solution of sodium chloride given intravenously. On the ninth day of this treatment the patient felt much better. Medication was supplemented by 30 drops of viosterol a day. On August 10 she became comatose and did not respond. However, she became conscious after 50 cc. of 50 per cent dextrose was given. Determination of blood sugar content taken the next morning with the patient in a fasting condition showed 35 mg. per hundred cubic centimeters. Thereupon the patient was maintained on dextrose given intravenously until her fasting sugar content rose to 122 mg. per hundred cubic centimeters, on August 14. Fluids high in sodium were also given.

By August 19 her blood pressure was 100 systolic and 70 diastolic, and therapy with adrenal cortical extract, which had been temporarily discontinued, was resumed. The patient felt much improved for several days. On August 23 there was another hypoglycemic reaction, which was relieved by administration of 25 per cent dextrose and 5 per cent dextrose in isotonic solution of sodium chloride. The dosage of desoxycorticosterone acetate was reduced to 0.5 cc. per day. Determination of blood sugar content taken at the time of this episode was 45 mg. per hundred cubic centimeters. On August 24 use of desoxycorticosterone acetate was discontinued. On August 26 there was another hypoglycemic reaction. The patient was unconscious and spastic, but she responded a half-hour after infusion of dextrose was begun. Use of desoxycorticosterone acetate was again resumed. These episodes of hypoglycemia recurred again despite intensive intravenous administration of dextrose in isotonic solution of sodium chloride. The patient was still unable to take solid food by mouth. At these times the blood sugar content was about 43 mg. per hundred cubic centimeters. On September 2 she was again unconscious, and 125 Gm. of sugar plus isotonic solution of sodium chloride was given without the patient's becoming conscious again. The blood sugar content at this time was 57 mg. per hundred cubic centimeters. An attempt was made to carry her along on dextrose and isotonic solution of sodium chloride, but she never fully regained consciousness, although there was one day when she appeared to recognize things about her. The patient went downhill, dying on Sept. 14, 1943.

The cardinal clinical symptoms of Simmond's disease were not noted in our patient except to the following limited extent. Cachexia or emaciation was not decided. The patient had lost weight but was not seriously emaciated. The atrophy of the buttocks, which has been

reported as striking in several cases (Escamilla and Lisser, 1942 [2]), was not decided. Premature aging was not prominent. The patient was 50 years but appeared about 55 or 60. Axillary and pubic hair was present but less abundant than normally. Genital atrophy or infantilism was not apparent. The blood pressure is frequently affected in Simmond's disease. Some patients have had mild hypertension, but others have suffered from severe hypotension, almost as low as that in Addison's disease. Postural hypotension has been stressed by one worker (Schellong, 1930, 1931, 1932). Our patient's most salient symptom was the extreme postural hypotension, so severe that on several occasions she lost consciousness when elevated from the reclining to the setting position. An extremely low basal metabolic rate characterizes Simmond's disease. Our patient's rate was + 12.5 per cent. The fasting sugar content has been reported as 60 mg. per hundred cubic centimeters or below in about 20 per cent of all cases. The fasting blood sugar content of our patient on several occasions was as low as 35, 43, 45 and 57 mg.

Postmortem Observations.—At autopsy, pathologic changes were found in the pancreas, adrenals and pituitary, by far the most striking changes being observed in the pituitary, which showed notable degenerative changes. The adrenals were smaller than normal; the cortices were narrowed and bore small deposits of hyaline material. The changes in the adrenals, however, were judged insufficient to account for clinical adrenal insufficiency. A detailed pathologic report is appended.

COMMENT

The patient here reported was a 50 year old woman with diabetes mellitus in whom the pancreas, thyroid, adrenal cortex and pituitary glands seem to have deviated from normal, to a greater or less degree. At the age of 19 she required a thyroidectomy for hyperthyroidism. At 38 she was found to be diabetic and required insulin in dosages as high as 35 to 50 units daily for a period. Three months before her death a hypopituitary-hypoadrenal syndrome, including hypoglycemic crises, developed. At autopsy, the pituitary gland was found to be almost completely destroyed, with secondary changes in the adrenal cortices.

The influence of her hyperthyroidism on the diabetes, which developed two decades later, is dubious, but the presence of the condition does reflect a dysbalanced endocrine organization of the body. Of cardinal interest in this case is the endocrine alteration which occurred later in her life, the mitigation of the diabetes mellitus by a condition clinically

2. Escamilla, R. F., and Lisser, H.: Simmond's Disease: Clinical Study with Review of Literature; Differentiation from Anorexia Nervosa by Statistical Analysis of 595 Cases, 101 Proved Pathological, J. Clin. Endocrinol. **28**:171-178, 1942.

resembling hypoadrenalism and pathologically falling best into the category of hypopituitarism with secondary hypoadrenalism.

With regard to the use of the word "coincidence," it should be explained that complete chronologic concurrence is not implied but rather the coexistence of the two diseases in the same patient at different periods. The diabetes is proved to have existed about three years before the appearance of the adrenocortical insufficiency and that of the anterior lobe of the pituitary. It was felt possible to assume that the gradual improvement in the diabetes, a disease with rare remissions, was due to the progressive development of the pituitary-adrenal syndrome.

THE PITUITARY AND DIABETES MELLITUS

The antagonism between the pituitary and the pancreas is one aspect of the complex relationship between them. The research of Houssay and his co-workers became the nucleus of all the experimental and clinical data now throwing light on this phase of carbohydrate metabolism.

Houssay and his co-workers in 1942 reviewed all the previous work on the pituitary carbohydrate relationship. The actions of the pituitary may be summarized as follows: 1. Hypophysectomy reduces the intensity of pancreatic and phlorhizin diabetes. 2. Hypophysectomy produces sensibility to the hypoglycemic action of insulin (and also to other hypoglycemic agents, including phlorhizin and fasting). 3. Anterior pituitary extract produces effects which are the opposite of the two previously noted. It increases resistance to hypoglycemic agents, and it aggravates diabetes. If the diabetes is the severe type resulting from complete pancreatectomy, it is intensified. If it is the milder diabetes found in dogs with both pancreas and pituitary removed, it is made much worse. In normal dogs, pituitary extract can produce diabetes. 4. Overactivity of the pituitary causes glycosuria evident in about one third of acromegalic cases. Some acromegalic patients, moreover, show increased resistance to insulin. 5. The pancreas after hypophysectomy has been shown to contain increased islet tissue in some animals. 6. Injections of pituitary extracts into animals produce varying effects on the pancreas. These are discussed in detail by Houssay.

The Houssay phenomenon refers to the disappearance of diabetes by means of hypophysectomy. Hypoglycemic crises occur frequently in animals with the Houssay phenomenon and can be prevented by injection of anterior pituitary extract.

We have been able to find 3 other cases in the literature in which the Houssay phenomenon has been spontaneously duplicated in human beings. In 1932 Calder [3] briefly mentioned a patient with Simmond's disease who before treatment had a type of sugar tolerance curve "characteristic

3. Calder, R. M.: Anterior Pituitary Insufficiency (Simmond's Disease), Bull. Johns Hopkins Hosp. **50**:87-114, 1932.

of a mild diabetes," on two occasions showing slight glycosuria. After treatment for the pituitary dysfunction "the sugar tolerance curve became normal and glycosuria disappeared."

Lyall and Innes,[4] in 1935, described a case of severe diabetes in a man aged 29 in whom much improvement in the diabetes became evident concurrently with the development of a pituitary lesion. His diabetes first manifested itself at 27 years, requiring 80 units of insulin daily. The insulin requirements, however, gradually declined. Six months later sugar tolerance tests showed diminished severity of the diabetes, and it was thought possible that an insulogenic adenoma of the pancreas was developing. Roentgenograms of the skull, however, showed a definite evidence of a pituitary tumor, "an abnormally dense deposit lying under the sella." A neurologic examination was noncontributory. When discharged from the hospital the patient remained sugar free and well without insulin. The nature of the pituitary lesion was still doubtful at the time of the authors' report, but they felt that it might be classified as a cystic adenoma which was becoming calcified or a meningioma arising from the dorsum sellae. This condition did not progress to spontaneous hypoglycemia.

A third instance of the Houssay phenomenon was reported by Kotte and Vonderahe [5] in 1940, that of a 40 year old man with diabetes mellitus of five years' duration who died of acute hypoglycemia. The diabetes had been diagnosed in an Irish hospital, had been treated by irregular administration of insulin "as the need arose" and was apparently of relatively mild severity. The patient was well until two months before his admission to the hospital, when loss of weight, easy fatigability and other symptoms developed, but he continued to work. Three days before his admission to the hospital a physician found that the urine contained "an excessive amount of sugar." He entered the hospital with "pallor, sweating, urinary incontinence and such excessive weakness that he could not talk above a whisper." He died eighteen hours after admission, having remained in a semistuporous state throughout hospitalization. Blood sugar levels, returned after death, were read at 31 and 20 mg. per hundred cubic centimeters.

The observations at autopsy revealed massive infarction with necrosis of the anterior pituitary, reported as "an area of partially disintegrated, pale staining cells implicating the entire anterior lobe except for a few normal glandular cells along some portion of the periphery." The pancreas and adrenals were normal both grossly and microscopically.

4. Lyall, A., and Innes, J. A.: Diabetes Mellitus and the Pituitary Gland: A Case of Diabetes with Intercurrent Pituitary Lesion and Concomitant Improvement of Diabetes, Lancet **1**:318-321, 1935.

5. Kotte, J. H., and Vonderahe, A. R.: The Houssay Phenomenon in Man: Report of Case of Diabetes Mellitus, Infarct of Anterior Lobe of Pituitary Body and Terminal Hypoglycemia, J. A. M. A. **114**:950-953 (March 16) 1940.

These are the only cases recorded of spontaneous development of the Houssay phenomenon in human beings. Some workers, however, have attempted to alleviate diabetes mellitus by roentgen therapy or surgical treatment directed at the pituitary. Since hypophysectomy reduces the severity of experimental diabetes, attempts have been made to produce similar results by means of heavy doses of roentgen rays. Cushing [6] (1932) successfully treated in this way a patient with pituitary basophilism showing hyperglycemia. This patient required 65 units of insulin daily, but after irradiation he became entirely sugar free on an ordinary diet without insulin.

Hutton [7] (1933, 1937 and 1939) has stated that he has successfully treated diabetes by irradiation of the hypophysis. In a series of about 50 patients he stated that "one third experienced no improvement of any kind; one third experienced symptomatic improvement, such as a decrease in headache, mental depression, nervousness and pains in the extremities, without any noteworthy change in the carbohydrate tolerance, and one third showed considerable improvement in carbohydrate tolerance, some being able, after treatment, to get along without insulin." No detailed data for these patients were given. This work is considered "unconvincing and inconclusive" (Rynearson and Hildebrand, 1941 [8]). Dobrin and Lucinian in 1935 [9] reported the trial of this technic in 3 children aged 12 to 16, without lasting benefit. Selle, Westra and Johnson [10] were unable to confirm the favorable results of irradiation in their studies of 7 diabetic (depancreatized) dogs.

Surgical ablation of the anterior lobe of the pituitary was attempted by Chabanier in 1936 [11] in a case of severe diabetes. Prior to operation the patient required from 150 to 170 units of insulin daily, the blood

6. Cushing, H.: Papers Relating to the Pituitary Body: Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932.

7. Hutton, J. H.: Irradiation of the Pituitary and Adrenal Glands in Essential Hypertension and Diabetes, Clin. Med. Surg. **44**:533-536, 1937; Roentgenotherapy of Endocrinopathies, Arch. Phys. Therapy **20**:287-293, 1939; Diabetes Mellitus and Essential Hypertension: Theory as to Their Etiology and Treatment, Illinois M. J. **64**:539-547, 1933.

8. Rynearson, E. H., and Hildebrand, A. G.: Metabolism and Diabetes: Review of Certain Recent Contributions, Arch. Int. Med. **68**:134-175 (July) 1941.

9. Dobrin, M., and Lucinian, H. H.: Diabetes Treated by Irradiation of Hypophyses, J. Florida M. A. **21**:550-551, 1935.

10. Selle, W. A.; Westra, J. J., and Johnson, J. B.: Attempts to Reduce the Symptoms of Experimental Diabetes by Irradiation of the Hypophysis, Endocrinology **19**:97-104, 1935.

11. Chabanier, H.; Puech, P.; Lobo-Onell, C., and Lelu, E.: Hypophyse et diabete (a propos de l'ablation d'une hypophyse normale dans une cas de diabete grave), Presse méd. **44**:986-989, 1936.

sugar content averaging 400 mg. per hundred cubic centimeters. After operation the blood sugar level ranged from 75 to 220 mg. per hundred cubic centimeters and the diabetes seemed improved, but the patient died five months postoperatively of pulmonary tuberculosis. The condition did not progress to spontaneous hypoglycemia.

An exhaustive review of the literature of Simmond's disease by Escamilla and Lisser [2] (1942) included an evaluation of sensitivity to insulin and of frequency of hypoglycemic coma. Among the 101 pathologically verified cases of Simmond's disease—all that could be found in the literature—hypoglycemic coma occurred in only 5. In 338 suggestive or typical clinical cases of Simmond's disease lacking pathologic investigation on the whole, only 1 case with episodes of hypoglycemic coma occurred. Frank diabetes mellitus has been reported in only 1 case of verified Simmond's disease, according to Escamilla and Lisser. No statement is made as to the alleviation of the diabetes by the hypopituitarism in this case.

THE ADRENALS AND DIABETES MELLITUS

The severity of diabetes in depancreatized animals can be alleviated not only by hypophysectomy (Houssay) but also by bilateral adrenalectomy. Another phenomenon analogous to that associated with the pituitary is found in the fact that injections of large quantities of adrenal cortical extract into adrenalectomized depancreatized animals increases the severity of diabetes (Joslin, 1940 [12]). Long and his co-workers have reported this work in a series of papers since 1934. They feel that hypophysectomy relieves diabetes by causing hypoadrenalism. This explanation is considered not completely tenable. Recent work by Long [13] (1940) suggests that not all the pituitary effect is so mediated but that the two hormones work synergistically.

Joslin (1940) pointed out that epinephrine exerts a significant effect on carbohydrate metabolism but an effect of only transient nature, "not fundamental in the sense that the anterior pituitary hormone is." Epinephrine increases glycogenolysis of the liver, thus opposing the formation of glycogen by insulin. The result is a rise in blood sugar content.

Injection of epinephrine by itself does not produce diabetes. There is, therefore, no condition analogous to pituitary diabetes. Moreover, the removal of the adrenal medulla does not improve the diabetes of depancreatized animals.

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12. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1940.

13. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309-344, 1940.

Denervation of the adrenals, celiac ganglionectomy or splanchnic nerve section have been found by deTakats and Cuthbert[14] (1932) to increase sensitivity to insulin in animals. Of 2 patients on whom bilateral splanchnic nerve section was carried out, 1 showed some improvement whereas the other was not benefited. Rogoff[15] (1936) reported a patient who underwent this operation, was not relieved of the diabetes and died in about a year of Addison's disease. The patient here reported clinically resembled a person with Addison's disease and at autopsy showed slight to moderate destructive changes in the adrenal. A brief survey of patients showing coincidence of diabetes and Addison's disease has been made, and 16 such patients have been found. The first well documented summary was reported by Arnett in 1927,[16] but Unverricht had mentioned a patient the year before. Arnett also reviewed five previous instances, all of which he considered questionable. Two patients were mentioned in a brief note from the Mayo Clinic (1930). Since 1930, instances of this association have been noted by Gowen[17] (1932), Simpson (1932), Crooke and Russell[18] (1935), Bloomfield[19] (1939), Rhind and Wilson[20] (1941) and McCullaugh[21] (1942). The unique case of Addison's disease produced by adrenal denervation reported by Rogoff in 1936 has been noted previously. Of these 16 cases, only 4 showed a decreased need of insulin because of the subsequently developing Addison's disease. Bloomfield's patient required only 4 to 6 units of insulin, although the original requirement was 40 units. McCullaugh's patient apparently displayed an almost full remission of diabetes.

SUMMARY

A patient with diabetes mellitus associated with hypopituitarism is reported. The patient's diabetes gradually improved as the hypopituitarism became severer, and she died after a prolonged course in the

14. deTakats, G., and Cuthbert, F. P.: Effect of Celiac Ganglionectomy on Sugar Tolerance of Dogs, Am. J. Physiol. **102**:614-619, 1932.

15. Rogoff, J. M.: Addison's Disease Following Adrenal Denervation in Case of Diabetes Mellitus, J. A. M. A. **106**:279-281 (Jan. 25) 1936.

16. Arnett, J. H.: Addison's Disease and Diabetes Mellitus Occurring Simultaneously, Arch. Int. Med. **39**:698-704 (May) 1927.

17. Gowen, W. M.: Addison's Disease with Diabetes Mellitus, New England J. Med. **207**:577-579, 1932.

18. Crooke, A. C., and Russell, D. S.: Pituitary Gland in Addison's Disease, J. Path. & Bact. **40**:255-283, 1935.

19. Bloomfield, A. L.: Coincidence of Diabetes Mellitus and Addison's Disease: Effect of Cortical Extract on Glycemia and Glycosuria, Bull. Johns Hopkins Hosp. **65**:456-465, 1939.

20. Rhind, E. G. G., and Wilson, A.: Diabetes Mellitus in Addison's Disease, Lancet **2**:37-38, 1941.

21. McCullagh, E. P.: Two Cases of Diabetes Mellitus, One with Myxedema, and One with Addison's Disease, Cleveland Clin. Quart. **9**:123-134, 1942.

hospital marked by several hypoglycemic episodes. The relationship among the pituitary, adrenal cortex and pancreas has been reviewed, with special reference to the so-called Houssay phenomenon. This is apparently the fourth recorded case representing this phenomenon.

DETAILED PATHOLOGIC REPORT

The body of this patient, examined one hour and twenty-five minutes after death, was that of a somewhat undernourished 50 year old woman whose cutaneous surfaces were pale. Superficially no significant pathologic changes were observed. The heart likewise showed nothing of note, but patchy acute bronchopneumonia was present in the lungs. The pancreas appeared smaller than normal, had a dull grayish white color and was softer than usual. On section the pancreatic lobules were indistinct. Histologically, the striking observation in the pancreas was the presence of decided sclerosis of both arteries and arterioles. Large foci of interstitial fibrosis were present. In these scars the acinar tissue was missing, but islets of Langerhans still remained. Small numbers of islets contained minute accumulations of hyaline material, which was present between the islet cells.

The adrenal glands were smaller than normal, and on section the cortical portions appeared thin and had a dull white color. The medullary portions were not remarkable. Histologically, decided arterial and arteriolar sclerosis was again evident. There were many extracapsular masses of cortical tissue, in some of which a hyaline material replaced the cells in the central portions. The capsules of the glands themselves were thickened, and the cortices were narrowed. Deep in the cortices were the same small deposits of hyaline material which were seen in the extracapsular cortical tissue. Histologically, neither gland presented enough destruction of the cortical cells to account for clinical adrenal insufficiency.

The pituitary gland, however, showed notable changes. Grossly it was larger than normal, and in the tissues of the anterior lobe focal hemorrhages were noted. Microscopically decided degenerative changes were found. There was a large zone of hyaline necrosis in the anterior lobe. In it were large numbers of cholesterol crystal clefts, many of which were surrounded by foreign body giant cells. Approximately four fifths of the anterior lobe appeared to be destroyed. In appearance the necrosis strongly resembled that found in large atheromas, such as sometimes occur in the aorta. About the periphery of this focus of necrosis were small numbers of anterior lobe cells whose outlines were indistinct and whose cytoplasm was vacuolated. Focal hemorrhages were present, and numbers of hemosiderin-filled macrophages were scattered throughout the viable portions of the anterior lobe. Small collections of lymphocytes and plasma cells were also noted near the junction of the anterior and posterior lobes.

PENICILLIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

A Study of the End Results in Thirty-Four Cases, with Particular Reference to Dosage, Methods of Administration, Criteria for Judging Adequacy of Treatment and Probable Reasons for Failures

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THE STUDIES concerned in this report were begun in July 1943 because of the belief that the previous failure of subacute bacterial endocarditis to respond to penicillin might be due to inadequate dosage and too short a period of treatment for a disease of this character.

To date 38 patients have been treated or are under treatment. The first 34 were selected for this report because the "recoveries" have been observed long enough for us to be reasonably sure of permanency in view of our accumulated experience. Relevant data on the first 20 cases are presented in the accompanying tables (tables 1 and 2). The first 4 cases of recovery (cases 3, 4, 5 and 8) were reported in June 1944.[1]

METHOD OF STUDY

Attempt was made to establish the approximate date of onset of the disease and the immediately predisposing illness such as infection of the upper respiratory tract, "influenza" or extraction of teeth. No patient was included in the study unless cultures of the blood yielded pathogens, even though clinical findings made the diagnosis likely. Laboratory examinations on the patients' admission

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Part of the penicillin used in this study was allocated by the National Research Council, part by the Penicillin Research Committee of Northwestern University and part by Schenley Laboratories, Inc., and Commercial Solvents Corporation.

1. (*a*) Priest, W. S., in discussion on Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Discussion on Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of One Hundred and Fifty Cases in Which It Was Employed, J. A. M. A. **125**:1003 (Aug. 12) 1944. (*b*) Priest, W. S., and Smith, J. M.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, Proc. Inst. Med. Chicago **15**:256 (Feb. 15) 1945.

to the hospital consisted in complete blood cell count; urinalysis; culture of urine; Kahn test; determination of the sedimentation rate, blood nonprotein nitrogen and chloride levels, carbon dioxide–combining power, total protein content and albumin-globulin ratio; tests of renal function; sulfobromophthalein test of hepatic function;

TABLE

Case	Sex	Age, Yr.	Duration of Disease, Wk.*	Organism	Sensitivity to Penicillin, Units/Cc.	Daily Dose of Penicillin	Number of Days on Each Dose	Anticoagulants	Number of Courses of Penicillin †
3	F	24	20	Str. viridans	0.06	200,000	(29)	Heparin	3
						200,000	(20)	Heparin	..
						200,000	(9)		
						450,000	(22)	Heparin	..
4	M	34	7	Str. haemolyticus	0.04	200,000	(27)	Heparin	1
5	M	21	15	Str. viridans	0.10	100,000	(3)	Heparin	2
						200,000	(24)	Heparin	
						200,000	(16)	Heparin	
8	F	44	16	Str. viridans	0.04	200,000	(14)	Heparin	1
						400,000	(15)	Dicumarol	
				.....	....	.....	....	.....	
			8 ††	.....	....	200,000	(9)	Heparin	
				Str. viridans	0.04	400,000	(29)	Dicumarol	1
10	F	32	12§§	Str. viridans	0.06	200,000	(28)	Dicumarol	..
						400,000	(28)	Dicumarol	2
11	M	74	10§§	Str. viridans	0.06	300,000	(28)	.....	..
						400,000	(25)	No anticoagulant	2
14	F	14	5½	Str. viridans	?	200,000	(16)	.....	..
						400,000	(29)	No anticoagulant	2
15	F	29	24	Str. viridans	0.02	100,000 to 150,000	(20)	No anticoagulant	..
						150,000 to 400,000	(60)	No anticoagulant	..
					0.02	500,000	(29)	No anticoagulant	3
16	M	44	13	Staph. albus	?	100,000	(11)		
						100,000 to 200,000	(20)	Dicumarol §	
						180,000	(7)		
						100,000 to 400,000	(26)		
						(12 days at 400,000)			4
18	M	53	6§§	Str. viridans	0.04	100,000	(2)	Heparin **	
						200,000	(4)		
						500,000	(33)		
						2,000,000	(50)	.....	1

* From date of first significant symptoms to beginning of course of penicillin which resulted in recovery. Cultures fr blood before such a course were positive for organisms regardless of previous penicillin therapy.

† By "course" is meant a period of treatment of seven days or more, separated from the next course by a seven days.

‡ Continuous intravenous drip by the method outlined in the text and interrupted intramuscular injection were the m used.

§ Used during first half of last course only.

determination of erythrocyte fragility and capillary fragility, and cultures of material from the nose and throat. Roentgenograms of the chest at 2 meters, electrocardiograms and dental roentgenograms of the whole mouth were made. Electro-

cardiograms were repeated at weekly intervals. The roentgenograms of the chest at 2 meters was repeated at the patient's discharge. Blood cell counts, urinalyses, determinations of the sedimentation rate and cultures of the blood were made frequently. Penicillin serum levels were determined and urinary excretion studied

...cured Patients

Total Units of Penicillin	Method of Administration ‡	Combined Sulfonamide Therapy	Complications	Time Elapsed Since Recovery at End of Last Course of Treatment as of Feb. 15, 1947, Mo.	Status as of Feb. 15, 1947
6,837,000	Intravenous	Sulfamerazine	Splenic infarct	32	Compensated; doing light housework
.....	Intravenous	Sulfadiazine			
	Intravenous				
5,600,000	Intravenous	None	None	35	Compensated; working 8 hr. day as chemist
5,200,000	Intravenous	None	Broca's aphasia; recovery	33	Compensated; working 8 hr. day at semisedentary work
.....	Intravenous	Sulfapyridine	Pulmonary embolism (?)		
2,800,000	Intravenous	Sulfapyridine	.....	26	Compensated; doing light housework
6,800,000	Intravenous	Sulfapyridine	None	26	Compensated; doing housework
6,400,000	Intravenous	Sulfapyridine	None	25	Compensated; doing light farm work
.....	Intramuscular	.....	.....	25	Compensated; doing normal schoolwork
25,006,000	Intravenous	Sulfapyridine			
.....	Intramuscular	Sulfadiazine			
.....	Intramuscular	.....	Phlebitis in the left leg		Compensated; 8 hr. day doing office work
2,800,000	Intravenous	Sulfapyridine	.....	24	
2,700,000	Intravenous	None	Pulmonary and cerebral embolism	28	Compensated; 8 hr. day doing office work
7,100,000	Intravenous	None	None	21	Compensated; continuing office practice (physician)

Used during fortieth to fifty-first and sixty-seventh to seventy-eighth days of treatment only.

Cultures from the blood were sterile and sedimentation rates normal for four months after termination of the first e; then the patient relapsed or was reinfected.

The patients in cases 10 and 11 were given second courses at increased dosage, because of rising sedimentation rates. In 8 the daily dose was increased to 2,000,000 units because, although cultures of the blood were sterile, the clinical condition extremely poor.

on many of the patients. A high caloric, high protein, high vitamin diet was given. In addition to administration of a multiple vitamin capsule of high potency, 100 mg. of thiamine hydrochloride, 50,000 units of vitamin A and 500 mg. of

TABLE

Case; Sex; Age, Yr.	Duration of Disease Before Any Penicillin Therapy, Wk.	Organism	Sensitivity to Penicillin, Units/Cc.	Daily Dose of Penicillin	Anticoagulants	Number of Courses of Penicillin	Total Days on Penicillin	Total Units Penicillin	Method of Administration
1 F 36	29	Str. viridans	0.02	Less than 200,000 (60 days) 200,000 (40 days)	Heparin *	16 †	100	17,556,000	Intravenous Intramuscular
2 F 17	11	Streptobacillus moniliformis	0.6	200,000 (5 days) 400,000 (14 days)	No anticoagulant	1	19	6,308,000	Intravenous Intramuscular Intrathecal
6 F 33	30	Str. viridans	0.04	200,000 (29 days) 300,000 (26 days)	Heparin Dicumarol	2	56	13,800,000	Intravenous
7 F 48	26	Str. viridans	0.02	200,000 (25 days)	Heparin	1	25	5,200,000	Intravenous Subcutaneous
9 M 65	9	Str. viridans	0.08	225,000 (28 days) 300,000 (27 days)	Dicumarol Heparin	2	55	14,425,000	Intravenous
12 F 34	42	Str. viridans	0.04	400,000 (30 days)	No anticoagulant	1	30	12,000,000	Intravenous
13 F 23	12	Str. viridans	0.04	100,000 to 200,000 (47 days) 300,000 to 400,000 (35 days) 500,000 (38 days) 980,000 (21 days) 1,000,000 (6 days) No penicillin (15 days) 2,000,000 (38 days) 1,000,000 (4 days)	No anticoagulant	2	204	144,305,000	Intramuscular Intravenous Intramuscular Intramuscular Intramuscular Intravenous Intravenous
17 M 69	25	Str. viridans	0.1	500,000 (29 days)	No anticoagulant	1	29	14,500,000	Intravenous
19 F 41	41 §	Str. viridans	1.0	300,000 (10 days) 200,000 (11 days) 250,000 (3 mo.) 500,000 (9 days)	Heparin ††	.. 4 **	.. 130	 27,000,000	Intravenous Intravenous Intramuscular Intravenous Intravenous
20‡‡ F 24	30 to 52	Staph. aureus	? §§	500,000 (8 days)	Heparin	2	8	4,000,000	

* During last nineteen days of illness only.
† From one to four days elapsed between "courses," except between numbers 15 and 16, when seven days elapsed (see
‡ During two "courses" only.
§ Before admission to our service.
** Beginning about three months after onset, patient received three of the courses elsewhere.

Method of Administration	Combined Sulfonamide Therapy	Clinical Complications	Postmortem Findings
ntravenous ntramuscular	Sulfadiazine ‡	Hemiplegia; infarcts of spleen and kidneys; bowel hemorrhage	Fibrous vegetations of moderate size covered with fibrin on the mitral valve; bacteria present
ntravenous ntramuscular ntrathecal	None None	Encephalopathy; choked disk	Fibrous vegetation of moderate size covered with fibrin on the mitral valve
ntravenous	None	Hemiplegia (recovery); infarcts of spleen and kidneys	Apparently healed vegetations of mitral valve; scarring and ulceration of left auricular wall; bacteria present
ntravenous ubcutaneous	None	Pulmonary embolism; atelectasis	Large vegetation on aortic valve; two vegetations at the base of pulmonary artery; all fresh and containing bacteria
ntravenous	None	Encephalopathy; uremia	Fibrous nodules on the mitral valve; ulcer on the tricuspid valve; microscopically still active, with bacteria
ntravenous	None	Congestive failure	Grossly completely healed mitral lesion; ruptured chordae tendineae; involvement of left auricular wall; microscopic thin layer of fibrin; no bacteria
ntramuscular ntravenous	Sulfapyridine	Renal infarcts; cerebral hemorrhage	Two small vegetations of mitral valve, grossly not active; involvement of left auricular wall; bacteria in lesion of the valve
ntramuscular ntramuscular ntramuscular ntravenous ntravenous			
ntravenous	None	Staph. aureus septicemia, terminal, after apparent cure of Str. viridans endocarditis	Several small red elevated areas on mitral valve; microscopically almost healed vegetations with fresh acute inflammation and masses of cocci
ntravenous ntravenous ntramuscular ntravenous	None	Congestive heart failure	No autopsy
ntravenous	None	Cerebral embolism; auricular fibrillation; congestive failure	No autopsy

Begun on the sixth day of therapy.
For about three weeks prior to admission to our service this patient received penicillin in daily doses of 100,000 to 200,000 intramuscularly, together with sulfadiazine. Figures given refer to therapy on our service only.
The original culture was lost before titration was done. Cultures of the blood after administration of penicillin was ed were sterile.

ascorbic acid were given daily. We believe that such supportive treatment is important in a relatively chronic wasting disease of this type.

The patients were unselected. No patient was refused treatment because of duration of illness or apparent hopelessness of condition.

AGE AND SEX INCIDENCE

The ages 8 to 74 are represented. The distribution according to decades is as follows: Forty-seven per cent fall into the two decades from 21 to 40, and 65 per cent fall within the decades from 21 to 50. There are 18 females and 16 males.

ETIOLOGIC FACTORS

In 22 cases (65 per cent) a definite history of infection of the upper respiratory tract, which merged into the symptoms of bacterial endocarditis, was obtained. In 3 patients the symptoms followed extractions of the teeth. Two of these had concomitant infections of the upper respiratory tract. It is generally accepted that some previous valvular damage is necessary to the development of subacute bacterial endocarditis. However, a definite or suggestive history of such could be obtained in only 19 cases (56 per cent). On the other hand, in all hearts examined at autopsy evidence of previous valvular damage was present.

VALVULAR INVOLVEMENT

In the patients who recovered the determination could only be clinical, but since the antemortem determination of valvular involvement was found to be correct in all patients on whom autopsies were performed (10 out of 12), we believe the clinical determination to be reasonably accurate. Valvular involvement was distributed as follows: mitral valve 27, or 80 per cent; mitral and aortic valves, 1, or 3 per cent; aortic valve 5, or 14 per cent, and mitral and tricuspid valves 1, or 3 per cent. One patient with aortic involvement also had vegetations in the root and ascending portion of the pulmonary artery (case 6).

BACTERIOLOGY

Organisms isolated included Streptococcus viridans (24 patients), Streptococcus haemolyticus (3 patients; in 1, non-green-producing, but only weakly hemolytic), nonhemolytic (gamma) streptococci (2 patients), Staphylococcus aureus (2 patients), Staphylococcus albus (1 patient), Streptobacillus moniliformis (1 patient) and Hemophilus parainfluenzae (1 patient).

The percentage of organisms (29 per cent) other than Str. viridans is higher than that usually reported.

Cultures of the blood were made routinely on admission, tests being made for both aerobic and anaerobic organisms and several different

mediums being employed for each procedure. Cultures were not reported as sterile unless there was no growth after fifteen days' incubation. When a culture was positive for organisms, the medium and procedure which had resulted in the best growth of the organism was used for subsequent cultures of the blood. Penicillinase [2] was added to the blood for culture to prevent false negative results due to penicillin in the blood. However, we have not obtained a culture yielding organisms from penicillinase-treated blood when sterile cultures resulted from the same sample of blood without penicillinase.

Adequate cultures of the blood permit early recognition of the disease and the institution of therapy before the pathologic processes have progressed too far. These should be made on all patients who do not recover promptly from simple infections of the upper respiratory tract, extractions of teeth, tonsillectomy and other minor ailments, particularly in patients known to have cardiac damage, however slight. It is our

TABLE 3.—*Concentration of Penicillin Required to Inhibit Growth of Organism in Vitro*

Seven organisms were lost before titration was done.

	Recovered	Deaths
0.06 units/cc. and under	7	5
0.07 units/cc. and over	9	5

conviction that the real solution of the problem of bacterial endocarditis lies in the prompt and adequate treatment of all known bacteremias plus the prophylactic use of penicillin in extraction of teeth and in every case of infection of the upper respiratory tract or any other infection in patients suspected of having valvular involvement.

After the organism was recovered and identified, it was titrated for sensitivity to penicillin according to the method of Hobby.[3] Results of tests for sensitivity in 26 cases ranged from 0.02 to 6.0 units per cubic centimeter. We have found the in vitro sensitivity to be only a rough guide of the daily requirements of dosage. The relationship between results of therapy and in vitro sensitivity to penicillin is shown in table 3. It is seen that in vitro sensitivity of the organism to penicillin is not per se significant as regards ultimate success of therapy. Previous duration of the disease and adequacy of the dosage of penicillin are more important prognostically than the in vitro sensitivity of the organism.

2. At first taka diastase (a proprietary starch digestant) was used and later penicillinase furnished by Schenley Research Laboratories.

3. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:277 (June) 1942. Later a modification of the method of Heilman and Herrell was used.[12]

Except when the organisms were of extremely high in vitro resistance, cultures of the blood usually became sterile within six to seventy-two hours after treatment with penicillin was started and remained so throughout therapy, regardless of whether or not the initially selected dosage was adequate for ultimate cure. The lack of significance of sterile cultures of the blood in judging response to therapy and adequacy of dosage will be discussed later.

METHODS OF ADMINISTRATION

Realizing at the onset that mere sterilization of the blood stream would probably not in itself be adequate for a cure in a disease in which bacteria are enmeshed

Fig. 1.—Needle anchored in small vein of forearm. Adapter and rubber tubing fixed to permit freedom of movement of forearm.

in fibrin and knowing from our own studies and those of others [4] that single doses of penicillin were rapidly excreted, with consequent rapid lowering of the blood level, it seemed logical that the maintenance of as constant a blood level as possible as well as one in excess of the in vitro sensitivity of the organism would be necessary. We therefore selected continuous intravenous drip as the method of administration most likely to insure a favorable result.

The day's dose of penicillin is dissolved in a liter of isotonic solution of sodium chloride and the rate of flow adjusted so that this amount is delivered in twenty-four hours.

4. Rammelkamp, C. H., and Keefer, C. S.: Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425 (May) 1943.

The method which we have found most satisfactory[5] has been described previously (fig. 1). It allows the needle to remain in situ for two weeks or longer without appreciable discomfort to the patient. Venous irritation and thrombosis did occur but were relatively infrequent. Five per cent dextrose or distilled water should not be used, since they promptly lead to such occurrences. The possibility of pulmonary embolism resulting from continuous venoclysis must be considered. However, since only 3 of the 12 patients on whom autopsies were performed had pulmonary emboli, which in all 3 could have been due to other conditions, we believe that the possibility is remote.

Recently we have been using a sodium salt containing 90 per cent penicillin X,[6] and so far there seems to be less venous irritation and thrombosis than with the regular sodium salt of various manufacturers. The same seems to be even more

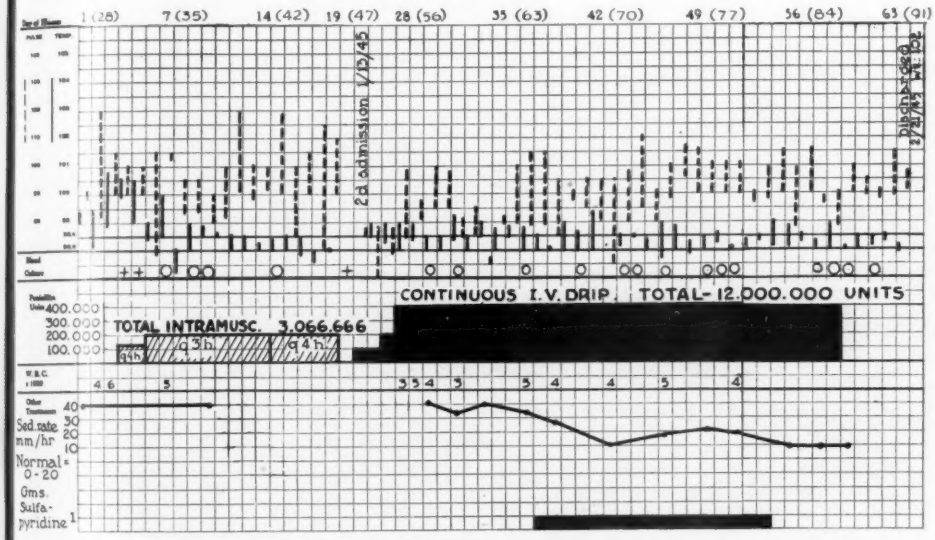

Fig. 2 (case 14).—J. W., aged 14 years, was admitted to the hospital Dec. 20, 1944, with a diagnosis of subacute bacterial endocarditis caused by Str. viridans. Figures in parentheses indicate the approximate days of illness.

definitely true of juxtacrystalline penicillin sodium containing 1,600 units per milligram.[7] The calcium salt (supplied by Schenley Laboratories, Inc.) also produces minimal venous irritation.

We are aware that cures have been and undoubtedly can be obtained by interrupted intramuscular injection even at three hour intervals. But from our experience to date, we believe that the highest percentage of cures will be obtained by

5. Priest, W. S.: Penicillin Therapy, Am. J. Surg. **67**:280 (Feb.) 1945. Herrell, W. E.: The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, J. A. M. A. **124**:622 (March 4) 1944.

6. Supplied by Lederle Laboratories, Inc.

7. Furnished by Commercial Solvents Corporation.

use of continuous intravenous drip. Cases 14 and 15 illustrate this point (figs. 2 and 3).

Permanently sterile cultures of the blood were not obtained in either case with intermittent intramuscular administration of daily doses of 300,000 to 500,000 units for prolonged periods. Cure was effected with continuous intravenous therapy. In addition, 3 other patients were cured following continuous intravenous therapy after failure had resulted on intramuscular injections of presumably adequate dosage and duration (300,000 units or more daily).

The serum penicillin levels obtained with similar daily doses administered by the two methods to the same person further suggest the apparent greater efficacy of continuous intravenous drip.

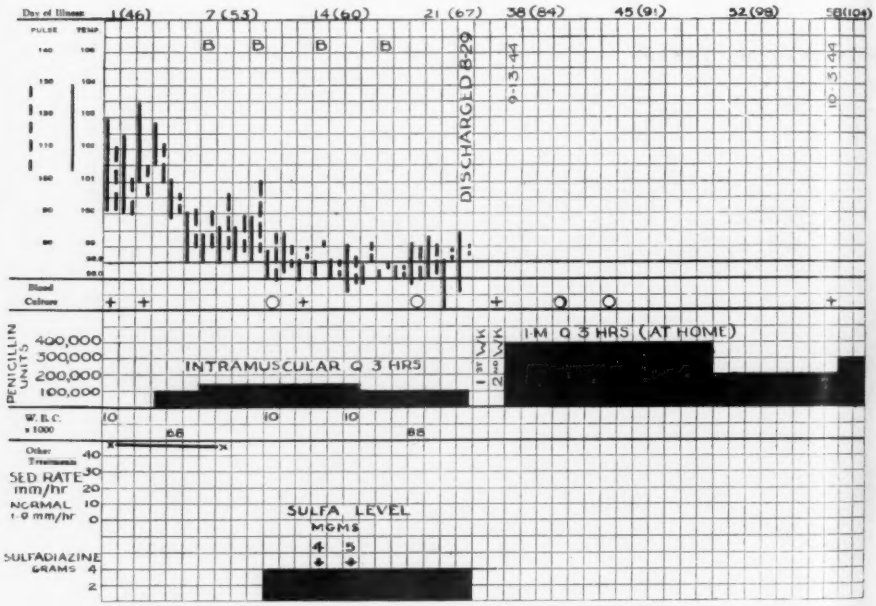

Fig. 3 (case 15).—M. K., aged 29, was admitted to the hospital on Aug. 7, 1944 with a diagnosis of subacute bacterial endocarditis caused by weakly hemolytic streptococci having a sensitivity to penicillin of 0.02 unit per cubic centimeter. *B* indicates transfusions of 500 cc. of whole blood. Figures in parentheses indicate the approximate day of illness.

In all but 2 of the successfully treated patients, so far, serum penicillin levels of at least 1 unit per cubic centimeter were found to be necessary. The level might occasionally fall to 0.5 unit per cubic centimeter, but if this level persisted for any length of time unfavorable clinical signs developed. In several instances favorable results could not be obtained until much higher levels were reached and maintained. When a single intramuscular injection of up to 80,000 units is given, the serum level rises rapidly to reach a maximum in about ninety minutes. From that point it falls rapidly, within thirty to forty-five minutes, to zero. Hence, in a three hour schedule of a daily dose up to 640,000 units there is a period of from

forty-five minutes to one hour out of every three when the serum level is below even the in vitro requirements for inhibition of the organism. Bacteriologic evidence of the possible importance of the period when the level is at zero, which occurs with intramuscular injection every three hours, was observed in our first patient (fig. 4). Daily cultures of the blood at various hours during the period of continuous intravenous drip failed entirely to yield organisms, while cultures taken three hours after an intramuscular injection occasionally produced them. This figure also illustrates the immediate and continuously sterile cultures of the blood obtained during administration of penicillin in dosages inadequate for cure. At autopsy, bacteria-filled fibrin was present on the incompletely healed valve. In this case the dose of penicillin remained the same for each period.

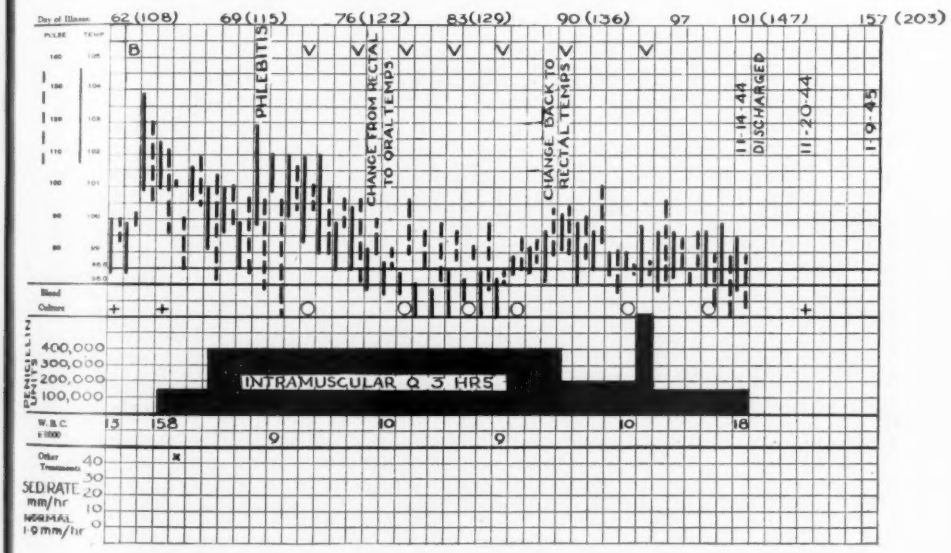

Fig. 4 (case 15).—The patient (fig. 3) was readmitted on Oct. 6, 1944. *V* indicates autovaccine. *B* indicates transfusion of 500 cc. of whole blood. Figures in parentheses indicate the approximate day of illness.

With administration of individual doses of 150,000 to 350,000 units, the outline of the serum penicillin curve is similar, but the maximum level is higher; the two hour level is usually theoretically adequate (1 to 2 units per cubic centimeter), and subminimal or zero levels are not reached until about three hours after injection. When 5 or 10 per cent dextrose in isotonic solution of sodium chloride is used as the diluent, the curves are the same so far as the duration of subminimal or zero levels is concerned. The maximum level, however, may be one and a half to two times as high as when the same dose is given in isotonic solution of sodium chloride to the same patient. The foregoing observations have been repeatedly confirmed. In 1 patient with renal insufficiency the lowest serum level with administration of 50,000 units every two hours was 2.0 units per cubic centimeter. This suggests the desirability of using diodrast or para-aminohippuric acid when interrupted intramuscular injection is the only feasible

method of administration. However, it seems more practical to use larger doses, 100,000 units or more, at intervals of not less than two hours and preferably at intervals of ninety minutes.

Determinations of the serum level done on the same patients when receiving penicillin by continuous intravenous drip in daily doses comparable to those given by interrupted intramuscular injection (300,000 to 2,000,000 units) show an absence of the high peak and the periods of subminimal or zero levels. There is some fluctuation, seldom exceeding 1 unit per cubic centimeter. Even with the smaller doses (300,000 to 350,000 units per day) the lowest level seldom is below 0.5 unit per cubic centimeter. Curves on the chart of the same patient on varying daily doses have the same features but at different levels. Doubling of the daily dose does not necessarily mean doubling of the mean serum level. The relatively constant serum levels obtainable by continuous intravenous drip constitute, we believe, the most important argument in favor of this method.

In doing these experiments, it was demonstrated that a relatively constant intake of fluid resulted in less fluctuation of the serum level, regardless of the method of administration. This led us to limit the oral intake of fluid to 800 cc. daily, given at the rate of 100 cc. every two hours from 7 a. m. to 9. p. m.

Continuous intrasternal infusion was tried on 1 patient who had previously received continuous intravenous drip. On the same daily dose comparable and equally constant blood levels were obtained. But after forty-eight to seventy-two hours the needle became loose. The method proved more uncomfortable for the patient.

Continuous subcutaneous infusion was used for thirteen out of twenty-five days of total treatment in 1 patient (case 7). Sterile cultures of the blood were obtained during this period; yet at autopsy the most active lesion of all was found. Unfortunately, studies of the blood level were not made on this patient. The organism was of the most sensitive group (0.02 unit per cubic centimeter).

Oral therapy, hourly dosage of 100,000 units of the preparations of penicillin then available being employed, failed to produce adequate blood levels, sterile cultures of the blood or the desired clinical improvement.

Intratibial infusion, because of the mechanical difficulties encountered, was abandoned, though it would apparently meet all criteria. In one out of five attempts it was successfully used for two weeks, producing blood levels equal to those obtained from continuous intravenous drip in the same patient.

DOSAGE AND DURATION OF TREATMENT

No uniformity of opinion exists as yet as to dosage and duration of treatment required. The facts relative to 20 patients in this series are set forth in tables 1 and 2. Regardless of other factors involved, cures resulted in only 2 cases from a dose of 200,000 units per day.

When the "courses" of treatment of less than three weeks' duration are excluded, these 20 patients received a total of forty-six courses, including those received prior to admission to our service. Twenty-one of these courses (45 per cent) were inadequate, regard less of dosage. Of these, 52 per cent were at the level of 200,000 to 250,000 units per day, 23 per cent at 300,000 units, 4 per cent at 400,000 units, 14 per cent at 500,000 units and 4 per cent at 2,000,000

units. Thus 75 per cent of the inadequate courses of treatment concerned doses ranging from 200,000 to 300,000 units per day. For this reason it is our opinion that administration of any daily dose less than 400,000 units is not conducive to the highest over-all percentage of cures. Further evidence that between 400,000 and 500,000 units per day is the minimal safe dose is the fact that 7 out of the 10 patients who recovered required this dose, after failing to respond to doses of 200,000 to 300,000 units, and 5 (50 per cent) of the deaths occurred in patients receiving 200,000 to 400,00 units per day and 3 in those receiving 500,000 units. These observations led us to adopt 500,000 units per day as the minimal initial dose when continuous intravenous drip is the method of administration.

The importance of adequate daily dosage from the outset is again stressed by comparison of the percentage of recoveries in our first and second groups of 20 patients. If from the first group we exclude the patient (case 12) who died of congestive failure but showed histologic evidence of cure and the 2 (cases 19 and 20) who lived only nine and eight days after being admitted to our service and on whom permission for autopsy could not be obtained and compare the rate of recovery with the first 17 of our second group of 20 patients, all of whom were started on 500,000 or more units per day, we find that 59 per cent of the first group are alive after twenty-one to thirty-five months and 88.2 per cent of the second group after thirteen to twenty months. Thus in the first group, in which 41 per cent died, all but 1 of those who died received less than 500,000 units per day, while in the second group in which only 11.8 per cent died, the daily dose was never less than 500,000 units and frequently 1,000,000 or 2,000,000 units. Duration of the disease prior to therapy and complications in the two groups were comparable.[8]

That the use of daily doses of less than 400,000 units has its unfavorable economic side is indicated in table 4, which shows the total units of ineffective or wasted penicillin and the total number of days in the hospital during which treatment was ineffective or wasted among 7 recovered patients who had received such dosage without favorable results.

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8. In vitro penicillin sensitivity of causative organisms was, on the whole, higher in the second group than in the first. Recovery was 100 per cent in cases 23 to 38 inclusive. The daily dosage adequate for recovery was 500,000 units in 4 patients and 1,000,000 units in 10 patients. Five instances of failure with 500,000 units per day are recorded. Recovery followed the use of larger doses. Two patients who failed to respond to daily doses of 1,000,000 and 2,000,000 units of penicillin recovered after administration of streptomycin. (Priest, W. S., and McGee, C. J.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **132**:124 [Sept. 21] 1946).

Our material does not permit of any definite conclusions as to the minimal optimum daily dose by interrupted intramuscular injection. From observations in cases 13, 14 and 15, from the failures which have resulted in our cases after long courses of 300,000 to 500,000 units per day and from our studies of serum penicillin levels following interrupted intramuscular injection, we should not feel safe in starting treatment with less than 800,000 to 900,000 units per day, divided into twelve or eighteen injections, when administration must be by this method.

One reason for the wide discrepancy in opinion as to what constitutes an adequate daily dose may lie in the wide variation of serum penicillin levels obtained in different patients from the same dose by whatever method given. In all our patients so far we have not observed

TABLE 4.—*Relation Between Daily Dose of Penicillin and Duration of Treatment in Cases of Recovery*

1. Average number of total days of treatment of patients started on less than 400,000 units per day	70
2. Average number of days of unsuccessful treatment with doses less than 400,000 units per day	43
(a) Maximum number of days of treatment before dose was increased to 400,000 or more units per day	168 *
(b) Minimum number of days of treatment before dose was increased to 400,000 or more units per day	6
3. Average number of days of treatment required for cure after administration of 400,000 or more units per day was started	32.0†
(a) Maximum	83.0
(b) Minimum	12.0
Total units of penicillin given without effect (round figures)	63,000,000
Total number of days in hospital during which treatment was ineffective	149
(The patient receiving one hundred and sixty-eight days of ineffective treatment was treated at home for one hundred and fifteen days)	

* During this period, this patient had thirty-six days at 400,000 units per day by interrupted intramuscular injection every three hours without securing permanently sterile cultures of the blood. Recovery occurred after thirty days at 500,000 units by continuous intravenous drip (case 15; fig. 3).

† When the 1 person (case 18) treated for eighty-three days continuously is omitted, the average is twenty-seven days.

a single cure in which the mean serum level was not considerably above 0.5 unit per cubic centimeter; yet only eight of twenty-six organisms titrated required more than 0.1 unit of penicillin per cubic centimeter for in vitro inhibition. The most obvious reason we can see for this discrepancy is the necessity for penicillin to penetrate deeply into the fibrin of the vegetative processes in order to inhibit the bacteria lodged there and the assumed lowering of concentration of the penicillin during such penetration.[9] That mere sterilization of the blood stream is not sufficient for a cure is now well established. Hence it would seem entirely possible to have in one series of patients a majority in

9. Since this article was written, experimental proof of this has been offered (Nathanson, M. H., and Liebhold, R. A.: Diffusion of Sulfonamides and Penicillin into Fibrin, Proc. Soc. Exper. Biol. & Med. **62**:83 [May] 1946).

whom adequate blood levels could be obtained with administration of 400,000 units per day or possibly less, while in another series adequate levels for the majority could be obtained only with administration of doses of 400,000 or more units per day. Since few physicians have the facilities or time to determine serum penicillin levels, it would seem all the more important to allow as much as possible for these variables and to start treatment with administration of a daily dose of at least 500,000 units.

How long treatment should be continued is another point on which all are not agreed. Having seen the degree of activity and the bacteria present in the lesions of 8 of the patients who died in this series and knowing that all 8 patients had had treatment from twenty days to several months and having observed in the patients who recovered that an average of twenty-seven days was required for clinical evidence of cure after adequate daily dosage was reached, we have adopted four weeks as the minimum duration of therapy. With one exception, anything less than four weeks of treatment has resulted in failure, regardless of dosage used. If clinical signs are not favorable at the end of this time, treatment is continued regardless of how many weeks it takes.[10]

The patients in cases 13 and 18 are the only ones of the first 20 to whom doses larger than 500,000 units per day were given. The patient in case 18 was doing badly clinically after thirty-three days at 500,000 units per day. The organism was relatively sensitive (0.04 unit per cubic centimeter) and duration of disease short (about eleven days). Whether a daily dose between the 500,000 units which was inadequate and the 2,000,000 units which resulted in a cure would have sufficed, we do not know. That the patient in case 13 should have had fibrin and masses of viable bacteria after eight months of treatment, forty-two days of which were at 2,000,000 units per day, remains an enigma.

The organisms from these 2 patients were typed as Streptococcus s.b.e.,[11] a strain of Str. viridans which is apparently peculiarly resistant to penicillin in vivo. Of the 7 patients whose organisms were typed as Str. s.b.e., 5 died. Our experience, as well as that of others,[11] indicates that when this strain is being dealt with the daily dose should be not less than 2,000,000 units.

These experiences have led us to take the position that if after four to six weeks' administration of 500,000 units per day

10. The average duration of treatment in cases 23 to 34 inclusive was fifty-seven days. This group included 4 patients in whom the situations were apparently hopeless at the outset of treatment. All recovered.

11. Loewe, L.; Plummer, N.; Niven, C. F., Jr., and Sherman, J. M.: Streptococcus s. b. e. in Subacute Bacterial Endocarditis, J. A. M. A. **130**:257 (Feb. 2) 1946.

by continuous intravenous drip the patient is not doing well clinically, then the dose is increased to 2,000,000 units per day. Subsequent experience may show that such a radical increase is not necessary, but from our evidence so far we are loath to do anything else. If the in vitro sensitivity of the organism can be determined before treatment is begun and it is found to be 1 unit or more per cubic centimeter, we start with administration of 1,000,000 units per day and do not hesitate to increase to 2,000,000 units and even higher doses per day if the clinical course is unfavorable.

Until more information is available on the relationship between duration of disease and response to therapy, we cannot say definitely how much this factor should influence the determination of the daily dose. The duration of disease in our patients who recovered up to the time of the course which resulted in recovery averaged sixteen and eight-tenths weeks, and that in the fatal cases to the time of initial penicillin therapy averaged twenty-two and one-half weeks. Our experience dictates that the minimal initial dose should be 500,000 units per day in any case and 1,000,000 units a day for any patient with a duration of disease of over twelve weeks.

REACTIONS

Thirteen of our first 20 patients had one or more reactions in the form of hyperpyrexia during therapy. These consisted of sudden severe chill with sharp rise in temperature to 103 up to 105 F. The return to normal always occurred within twelve hours. There was no relationship to the brand of penicillin used. The transferring of the penicillin and isotonic solution of sodium chloride, rubber tubing and needle intact to another patient failed to produce a reaction in the second patient. Hence it was concluded that it could not be due to pyrogens. The dosage of penicillin per se was not the cause, since reactions occurred with administration of 200,000 units per day as well as with 1,000,000 units per day. Two patients (cases 8 and 10) had several reactions during their first course at 200,000 units per day but had none during a second course at 400,000 units per day. Another patient (case 6) had none on a daily dose of 200,000 units but had several during a second course at 300,000 units per day, initiated several weeks later. Other patients in whom more than one level of dosage was used had reactions at both levels. It is of interest, although of doubtful significance, that of the patients who recovered (clinically and histologically) 73 per cent had these reactions while of those who failed to recover only 55 per cent had these reactions. One cubic centimeter of serum obtained from a patient at the height of a reaction and reinjected during an afebrile period produced the same type of reaction in a most violent form, whereas her "normal" serum did not. This

would seem to indicate an individual anaphylactoid phenomenon. Febrile reactions have not occurred in our latest 13 patients even with administration of doses up to 2,000,000 units per day. This suggests that something in the earlier penicillin salts which is not now present may have been the cause. Except in 1 case, we could not detect any harm to the patient by these reactions and did not discontinue treatment.

Urticaria was observed once (case 8). This was at the outset of a second course of treatment instituted because of a relapse after five months of apparent cure. It was not widespread, treatment was not discontinued and the urticaria disappeared within a few days.

A disconcerting type of reaction, encountered four times thus far, is abdominal pain, sometimes of great severity, associated with tenderness, usually generalized, rigidity and distention. In all instances careful examination failed to reveal any intra-abdominal, gastrointestinal or renal lesion, and the symptoms promptly subsided on withdrawal of penicillin. From our meager experience with this reaction it appears possible to resume therapy after a few days, without recurrence of reaction.

COMBINATION THERAPY

None of the strains of Str. viridans encountered in all our patients to date has been inhibited in vitro by any of the sulfonamide drugs. In cases 1, 3 and 15 sulfadiazine was used in full therapeutic doses without affecting the cultures of the blood. The patient in case 3 also had a short course of sulfamerazine. The patients in cases 3, 8, 10, 11, 14 and 15 of the group which recovered had subtherapeutic doses (1 to 2 Gm. per day) of sulfapyridine during penicillin therapy. In these patients recovery followed the course of penicillin in which such doses of sulfapyridine were also given. However, in each instance the daily dose of penicillin was also increased; hence it cannot be said that the addition of the sulfapyridine was a deciding factor in recovery. No synergistic effect was observed when the organisms from several of these patients were subjected in vitro to combinations of penicillin and various sulfonamide compounds in varying concentrations.

From these in vitro tests and from the several instances in which sulfonamide drugs were of no help when used in connection with doses of penicillin later proved to be inadequate, we are of the opinion that, so far as Str. viridans is concerned, the use of sulfonamide drugs in connection with penicillin is without value. In fact, we believe that the use of sulfonamide drugs is contraindicated because of the frequent involvement of the kidneys by the disease itself. However, that one must be on the lookout for the unusual organism which will respond only to combined administration of the two drugs is indicated by 1 of our patients whose organism belonged to the parainfluenzal group. Sterile cultures of the blood and clinical improvement could not

be obtained with eight weeks of administration of penicillin alone in doses up to 1,000,000 units per day. Sulfonamide therapy alone was equally ineffective.[12] Use of a combination of 500,000 units of penicillin and sulfamerizine to maintain a blood level of 10 to 22 mg. per hundred cubic centimeters for a period of forty-three days resulted in arrest of the disease. It is now seventeen months since completion of this combined therapy, and there have been no signs of relapse.

ANTICOAGULANTS

The use of anticoagulants (heparin as well as dicumarol [3,3′-methylene-bis-(4-hydroxycoumarin)] proved of no demonstrable therapeutic value.[13] They exerted no influence on the dosage of penicillin, had no influence on the formation of fibrin, as shown in histologic studies, and did not affect the length of time over which therapy was required.

OTHER FACTORS IN RELATION TO SUCCESSFUL OR FATAL TERMINATION

As noted in the section "Method of Study," several collateral observations were made on the patients in this series. The total data on any one factor were found to be too small to permit of statistical evalution. The actual results will therefore be presented without much comment.

1. *Age.*—The average age at the time of beginning therapy of those who died was 39.0 years, and of those who recovered it was 33.5 years.

2. *Average Duration of Disease Before Administration of Penicillin.*—In those who died, the average duration was 22.5 weeks; in those who recovered it was 9.2 weeks. The latter figure loses much of its apparent significance when the average duration of disease among the patients with successful results is adjusted to the time of the final course of therapy which actually resulted in cure, when one bears in mind that up to that time the disease in these patients was bacteriologically or clinically active and that they would presumably have died had it not been for this final successful course. With such adjustment the figure becomes 16.8 weeks.

3. *Erythrocyte Count.*—In the fatal cases the average was 3,350,000 before administration of penicillin; in the cases of recovery it was 4,230,000.

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12. This organism was insensitive to any concentration of penicillin in vitro but was inhibited by a sulfonamide concentration of 3 mg. per hundred cubic centimeters. It was later found to be inhibited by streptomycin, which today would be the drug of choice for such an organism.

13. Priest, W. S.; Smith, J. M., and McGee, C. J.: The Effect of Anticoagulants on the Penicillin Therapy and Pathologic Lesion of Subacute Bacterial Endocarditis, New England J. Med. **235**:699 (Nov. 14) 1946.

4. *Leukocyte Count.*—The average in the fatal cases before administration of penicillin was 11,000; after administration of penicillin it was 13,700. The average in the cases of recovery before administration of penicillin was 8,880; after administration of penicillin, it was 9,200. In addition to suggesting that patients with a normal leukocyte count before therapy have a better prognosis than those with leukocytosis, it also emphasizes what will be stressed later—that a rise in leukocyte count occurring during or immediately after therapy is indicative of inadequate treatment unless some other definite cause can be found for the rise.

5. *Total Serum Protein Content.*—In all patients the total serum protein content was at or slightly below the lower limit of normal before penicillin therapy. In the fatal cases the average level remained unchanged, while in the cases of recovery there was a slight increase (averaging 0.64 Gm. per hundred cubic centimeters) after penicillin therapy.

6. *Albumin-Globulin Ratio.*—The albumin-globulin ratio was close to 1 : 1 or slightly dislocated in all patients before therapy. Little change occurred during therapy in either the cases of failure or the cases of recovery.

7. *Alkali Reserve.*—Slightly subnormal values were found in all patients before penicillin therapy. During therapy there was essentially the same rise in carbon dioxide–combining power (3.8 to 3.5) in both cases of failure and cases of recovery.

8. *Blood Chloride Levels.*—Blood chloride levels were within normal range in all patients before therapy.

9. *Electrocardiographic Changes.*—Serial records made during therapy showed a preponderance of changes in the patients who died. Of these, only 1 failed to show electrocardiographic changes. The observed changes (except those induced by digitalis) were shift in the electrical axis, inversion of the T wave in leads III and CF_2, changes in the T wave suggestive of coronary insufficiency, flattening of the T wave in all leads and the development of arrhythmias (auricular fibrillation and ectopic impulses). Serial records of 16 patients who recovered showed no change in 13, and changes in the T waves and RS-T interval in 3. From this it would seem that serial electrocardiograms are of value as an aid to prognosis and possibly in estimation of the degree of myocardial involvement during the course of the infection. To date, the hearts of the 3 recovered patients who showed electrocardiographic changes are not demonstrably less efficient than the hearts of those whose records showed no changes.

10. *Complications.*—As to renal, splenic, pulmonary and cerebral infarction, meningoencephalopathy, the development of cardiac arrhyth-

mias and thrombophlebitis (not caused by intravenous therapy) there was a total of fifty-seven such complications. Thirty-seven of these occurred in the patients who died. It is possible that small infarcts of the spleen, kidneys and lungs were missed in the patients who recovered whose records contained no evidence of such and in cases in which the patient's complaints did not suggest them. However, it seems safe to say that in cases in which the infarct is of sufficient size to cause clinically recognizable symptoms and signs and if such episodes are multiple, the prognosis is less favorable.

We wish to call particular attention to a cerebral complication we have observed twice. Signs of meningeal irritation develop. Intracranial pressure is increased to the point of papilledema. The spinal fluid is under increased pressure and the cell count and protein content are increased, but organisms are not found. Cranial palsy of the nerves, particularly of the oculomotor nerves, may occur. Headache, photophobia and dimness of vision were complained of, and vomiting occurred in both patients. A diagnosis of brain abscess, possibly multiple, was made. Yet at autopsy of 1 patient no abscess was found. Intraspinal injection of penicillin in doses up to 50,000 units daily had no effect on the course of the disease or the cerebral symptoms in this patient. Our belief that the daily intravenous dose of penicillin in this patient should have been at least 2,000,000 units is based on our experience with the second patient having similar symptoms. In this patient a diagnosis of brain abscess was also made, and unsuccessful attempts were made to localize it by ventriculography. Intracranial pressure became so great that decompression was necessary. With administration of adequate doses of penicillin (2,000,000 units per day) the patient progressed to recovery and, except for minor residual neurologic effects, appeared normal seventeen months after termination of therapy. Dr. Frederick Hiller, of the Department of Neurology, who examined most of our patients showing cerebral complications, stated the belief that these phenomena represented meningoencephalitis caused by multiple minute bacterial emboli. He expressed the opinion that in subacute bacterial endocarditis cerebral manifestations are the result of large emboli or metastatic mycotic encephalitis. The latter is more frequent and is caused by minute bacterial emboli. Appearance of areas of ischemia followed by acute inflammatory reaction and possibly hemorrhage result. The surrounding brain tissue is edematous. The clinical picture may vary from that of a sudden transitory aphasia or monoparesis to a hemiplegia. The ability of the brain to recover from this type of lesion is remarkable. Even complete hemiplegia may disappear in a few days, with little or no residuals. Showers of such bacterial emboli may produce coma, delirium and convulsions. Such lesions occurring in

the meninges add signs of meningitis to the picture, which may be further aggravated by hemorrhage into the subarachnoid space.

If recovery from hemiplegia is slow and significant residual paresis remains, the lesion is most likely an embolism of a larger arterial branch. If bacteria are present in such a major embolus, an abscess might develop. However, the relative avirulence of most organisms responsible for subacute bacterial endocarditis makes brain abscess extremely rare in this disease, and surgical treatment is almost never indicated. The

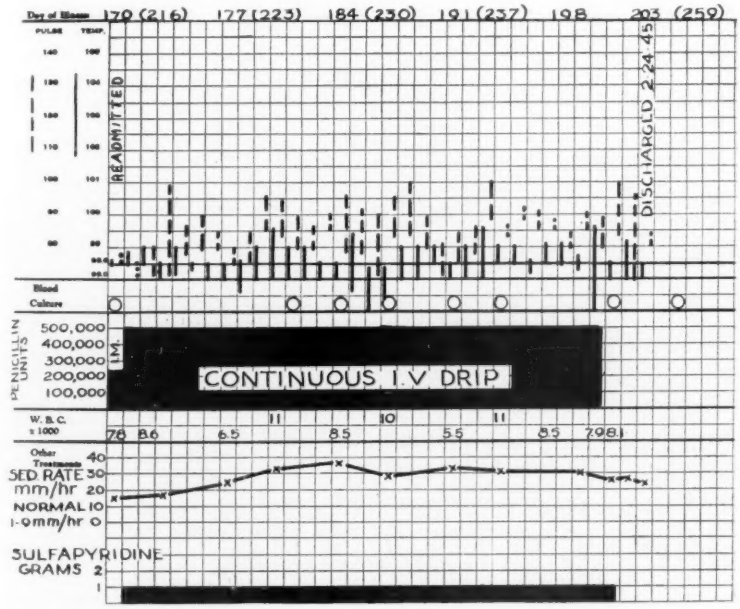

Fig. 5 (case 15).—The patient (figs. 3 and 4) was readmitted on Jan. 22, 1945. The figures in parentheses indicate the approximate day of illness.

condition calls for administration of large doses of penicillin (1,000,000 to 2,000,000 units or more per day).

CRITERIA FOR SUCCESS OF THERAPY

Any one undertaking penicillin therapy of subacute bacterial endocarditis for the first time is confronted with the problem of how much penicillin should be used, for how long and how it will be indicated that the patient is cured. Our opinions concerning dosage and average duration of treatment and the reasons therefor have already been set forth. The unreliability of sterile cultures of the blood, normal temperature and the patient's sense of well-being as criteria of success or

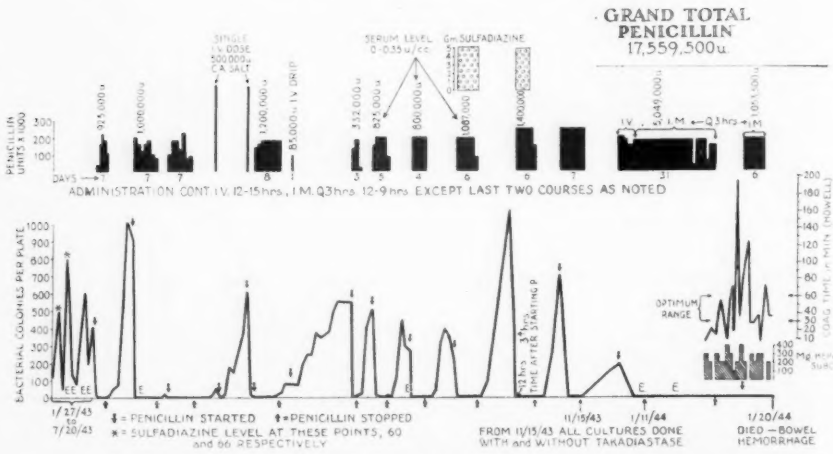
GRAND TOTAL
PENICILLIN
17,559,500 u.
ADMINISTRATION CONT. I.V. 12-15 hrs., I.M. Q3 hrs. 12-9 hrs. EXCEPT LAST TWO COURSES AS NOTED
BACTERIAL COLONIES PER PLATE
OPTIMUM RANGE
1/27/43 to 7/20/43
↓ = PENICILLIN STARTED ↑ = PENICILLIN STOPPED
* = SULFADIAZINE LEVEL AT THESE POINTS, 60 and 66 RESPECTIVELY
FROM 11/15/43 ALL CULTURES DONE WITH and WITHOUT TAKADIASTASE
11/15/43
1/11/44
1/20/44
DIED — BOWEL HEMORRHAGE

Fig. 6 (case 1).—Mrs. E. S. had subacute bacterial endocarditis caused by Str. viridans having a sensitivity to penicillin of 0.02 unit per cubic centimeter. *E* indicates visceral embolic phenomena.

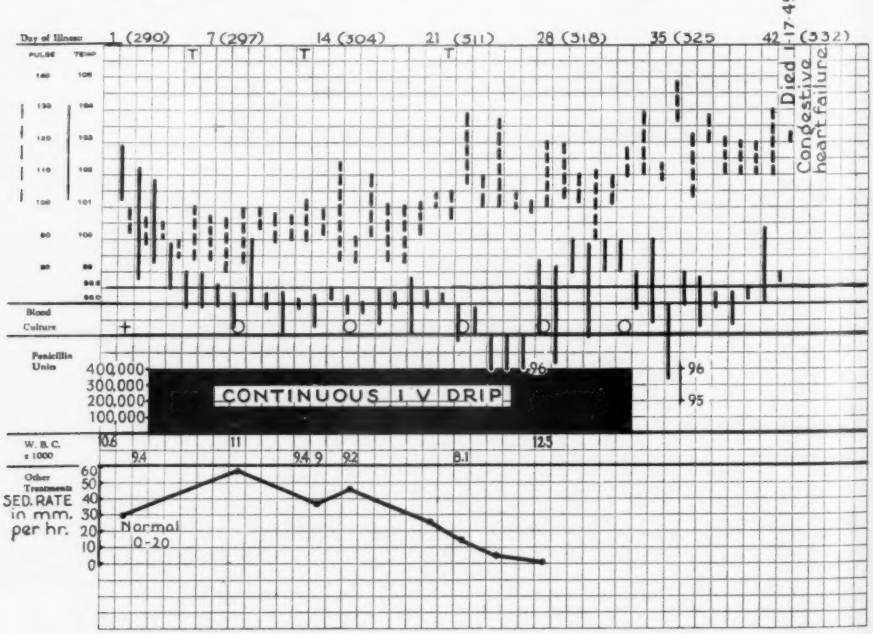

Fig. 7 (case 12).—Mrs. H. B., aged 34, was admitted to the hospital on June 12, 1944 with a diagnosis of subacute bacterial endocarditis caused by Str. viridans with a sensitivity to penicillin of 0.04 unit per cubic centimeter. *T* indicates blood transfusions of 500 cc. Figures in parentheses indicate the approximate day of illness.

adequacy of therapy have also been pointed out. Of course, a culture of the blood which produces organisms during therapy always means that the daily dosage is dangerously inadequate, since dosage may be inadequate though cultures of the blood become sterile. The only consistently reliable guides we have found after cultures of the blood have become sterile are the leukocyte count and the sedimentation rate.

As stated before, the leukocyte count in the fatal cases averaged 2,700 higher after penicillin therapy than before, while the average of the cases with successful results was unchanged. In the first 20 cases there were 14 instances in which an elevated or rising leukocyte count was followed

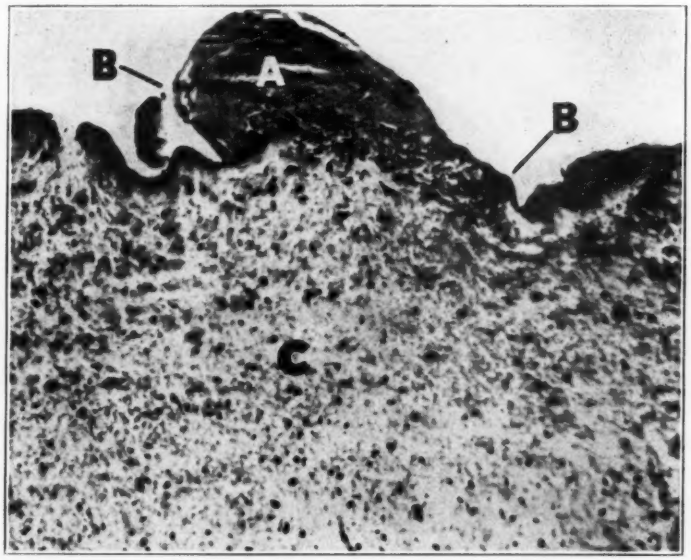

Fig. 8—Section of mitral valve of patient in case 12. *A*, thin layer of organizing fibrin free of bacteria. *B*, proliferating endocardium. *C*, organized and organizing scar tissue. × 60.

by or coincided with cultures of the blood yielding organisms. In addition, there were 2 instances in which a rising leukocyte count as an indication of activity was proved by the findings at autopsy. Less frequently occurring, but of significance is the fact that a normal leukocyte count may be obtained in the presence of a culture of the blood yielding pathogens and histologic evidence of activity. While we cannot conclude that a normal leukocyte count is an indication that all is well, we do believe that, unless explained by some complicating factor, a persistently elevated leukocyte count or a steadily rising one during treatment is a reliable indication that dosage is inadequate or that treatment should

be continued further or both. If after treatment has been stopped the leukocyte count rises steadily, we consider this a definite warning, and if coincidentally the sedimentation rate rises immediate further treatment, and, generally speaking, with considerably larger daily doses, is impegative.

In these same 20 cases there were 19 instances in which a sedimentation rate of 20 or over (Wintrobe and Westergreen) coincided with activity, as proved by either cultures of the blood which produced organisms or the postmortem finding of bacteria-filled fibrin on the valves. There were 8 instances in which a steadily rising sedi-

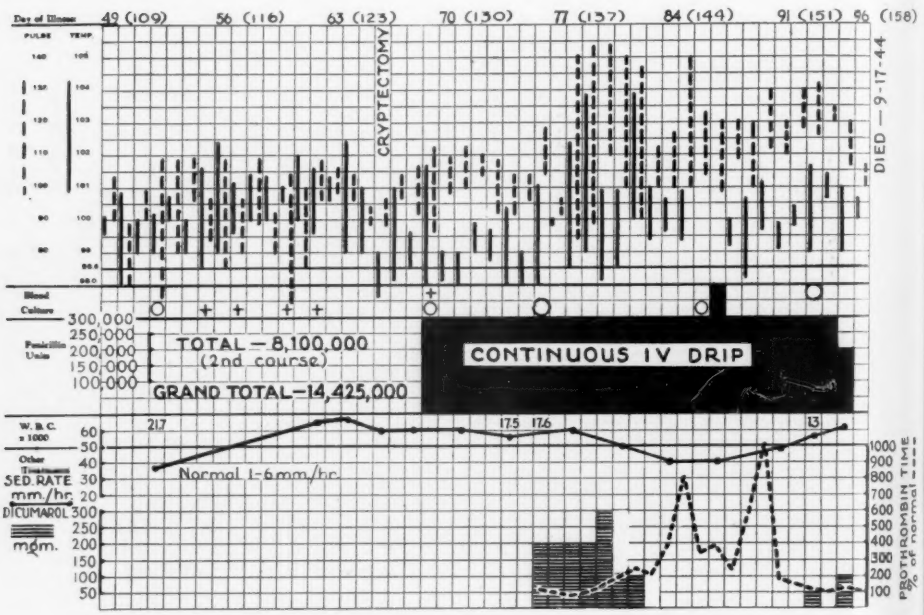

Fig. 9 (case 9).—H. P., aged 65 years, had subacute bacterial endocarditis caused by Str. viridans having a sensitivity to penicillin of 0.08 unit per cubic centimeter. Figures in parentheses indicate the approximate day of illness.

mentation rate, either during or after treatment, preceded the reappearance of pathogens in cultures of the blood or death, after which active lesions containing bacteria were found. The rise was from a normal level in 4 instances and from an elevated level in 4. All our recovered patients had normal or nearly normal sedimentation rates on discharge from the hospital or else had slightly elevated rates which steadily declined to normal over a period of a few weeks after discharge. The only exception to this in all our patients so far has been one who, although free of evidence of endocardial infection eight months after com-

pletion of therapy, has rheumatoid arthritis. Histologic proof of the relationship between a sedimentation rate which steadily declines to normal and healing of the lesion is afforded by case 12 (fig. 5). In this case the organizing process was virtually complete, the integrity of the endocardium was almost reestablished and only scattered microscopic

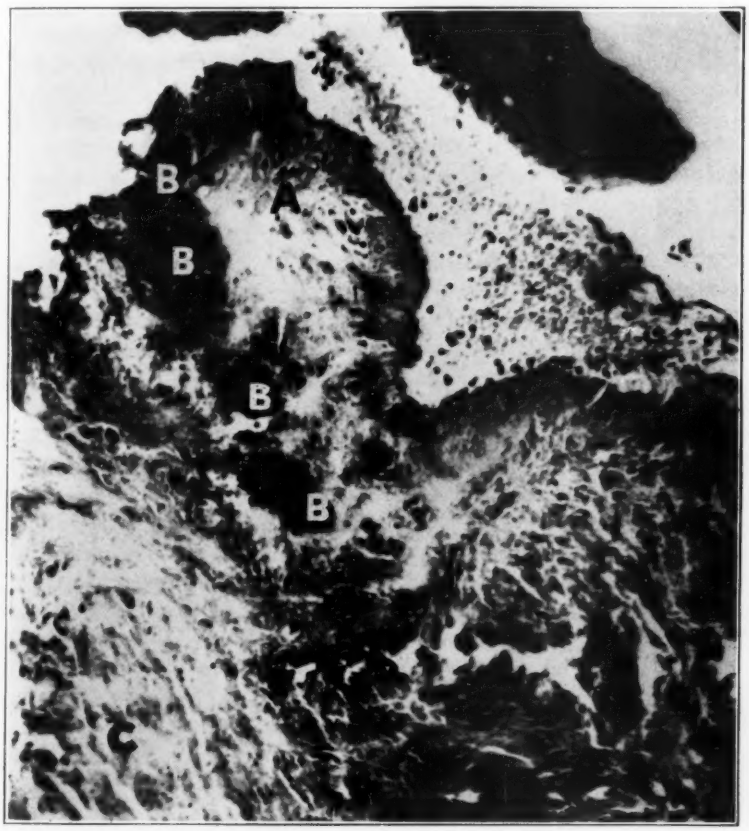

Fig. 10.—Section from an active lesion of the mitral valve of the patient in case 9. *A*, fibrin. *B*, clumps of cocci on the surface of and buried deeply in the fibrin. *C*, organizing scar tissue. × 60.

areas of bacteria-free fibrin were found (fig. 6). Death was due to congestive cardiac failure. Histologic proof of the relationship between leukocytosis and persistently elevated and rising sedimentation rate and an active bacteria-laden lesion, in spite of sterile cultures of the blood, is illustrated in figures 7 and 8. All patients showing active lesions at

autopsy had elevated sedimentation rates at the time of death. If we accept a sedimentation rate of 20 or over as indicating activity before therapy, it is illogical not to accept the same interpretation after therapy. At this point the elevation may mean only the persistence of fibrin or inflammatory reaction and not necessarily bacteria. But it is our conviction that until the sedimentation rate returns to normal these patients cannot be considered out of danger, and cultures of the blood, leukocyte counts and determinations of the sedimentation rate must be made at frequent intervals. These observations were confirmed in 14 of the subsequent cases.

After trying various methods for determining the sedimentation rate, we adopted that of Wintrobe, which permits of ready correction for the hematocrit reading.

SUMMARY AND CONCLUSIONS

The end results in 34 unselected cases of subacute bacterial endocarditis in which the patients were treated with penicillin are reported. Twenty-two (65 per cent) are alive and free of any evidence of the disease from thirteen to thirty-five months after completion of treatment.

Duration of the disease ranged from one and a half to fifty-two weeks before admission to our service.

Str. viridans predominated as the offending organism, but six other organisms were encountered. In vitro sensitivity of the organisms in 27 cases ranged from 0.02 to 6.0 units per cubic centimeter.

Administration of penicillin in isotonic solution of sodium chloride by continuous intravenous drip was found superior to intermittent intramuscular injection, in the maintenance both of constant adequate blood levels and of the patient's comfort. Five per cent dextrose in isotonic solution of sodium chloride was found much more likely to produce troublesome venous irritation and thrombosis.

Restriction of the intake of fluids to 800 or 900 cc. during the waking period resulted in less wide fluctuation of the serum penicillin level.

To increase the dose of penicillin seems simpler to us than to use para-aminohippuric acid or diodrast to retard the rate of excretion from the kidneys.

No clinical or histologic evidence was found to favor the use of anticoagulants. The danger of fatal hemorrhage suggests caution in their use.

Success of treatment was judged by clinical, laboratory and histologic evidence.

Adequate daily dosage over a sufficiently long period is the most important single factor in success of treatment. With the use of continuous intravenous drip, the minimal safely efficacious dose is 500,000

units per day, with administration of 1,000,000 to 2,000,000 units per day or more if clinical criteria dictate or if the disease is of over twelve weeks' duration. Daily dosage of 500,000 or more units at the outset has resulted in recovery of 100 per cent of 16 consecutive patients, as compared with 59 per cent (adjusted figures) in the first 20 patients, in which 7 of the 10 deaths occurred in patients receiving 400,000 units or less. If intermittent intramuscular injection is the only feasible method, minimal doses of 100,000 units at ninety minute intervals are recommended. Treatment should be continued for not less than four weeks.

Conclusive evidence, either in vitro or clinical, of the synergistic effect of the sulfonamide drugs was found in only 1 patient. The organism belonged to the parainfluenzal group.

In vitro sensitivity of the organism has little bearing on the outcome but is a rough guide as to the daily dose. A minimal daily dose of 1,000,000 units or more is recommended when one is dealing with organisms sensitive to only 0.1 unit or more in vitro. The possibility of the presence of a strain of Str. viridans particularly resistant in vivo should be considered as a cause of failure not otherwise explainable. A minimal daily dose of 2,000,000 units for this organism seems essential.

The most reliable indexes of successful therapy and adequacy of therapy were found to be the leukocyte count and the sedimentation rate. Sterile cultures of the blood cannot alone be considered conclusive, as they do not indicate control of the valvular lesions. These points, as well as daily dosage, in relation to the findings at autopsy will be discussed in detail in a subsequent publication.

All recovered patients were observed (blood cell counts, sedimentation rates, cultures of the blood and physical conditions) at weekly intervals during the first month after discharge, thereafter semimonthly for six months and then monthly to date.

The residents, interns and medical clerks of Wesley Memorial Hospital aided in this work.

Correspondence

ASSOCIATION OF PNEUMONIA WITH ERYTHEMA MULTIFORME EXUDATIVUM

To the Editor:—Readers of the article entitled "Association of Pneumonia with Erythema Multiforme Exudativum," published by the Commission on Acute Respiratory Diseases in the ARCHIVES (**78**:687 [Dec.] 1946), may be confused by the failure of the authors to distinguish the syndrome which they describe from another with a similar name but quite different clinical characteristics. Osler, some fifty-two years ago, published a paper (*Am. J. M. Sc.* **110**:629 [Dec.] 1895) entitled "On the Visceral Complications of Erythema Exudativum Multiforme," in which he described 11 cases of a polymorphic syndrome which included a variety of cutaneous and visceral lesions. This clinical picture was distinctly different from that described in your journal.

In Osler's cases hemorrhagic lesions of the skin and the mucous membranes were outstanding, although cutaneous involvement also included erythema, edema and urticaria. Visceral manifestations included gastrointestinal crises, nephritis, pericarditis, possible endocarditis, splenomegaly and "bronchitis." Articular and periarticular swelling also occurred. If studied under modern conditions some of Osler's cases would probably be classified as anaphylactic purpura, acute idiopathic purpura with thrombopenia, rheumatic purpura, acute polyarteritis nodosa, acute disseminated lupus erythematosus, etc.

It seems clear that Osler and the Commission on Acute Respiratory Diseases were not describing the same syndrome, despite the similarity of terminology, and it is hoped that confusion will be a little less confounded as a result of this minor animadversion.

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Hospital of the University of Pennsylvania.

News and Comment

GENERAL NEWS

American Society for Research in Psychosomatic Problems.—The Fourth Annual Meeting of the American Society for Research in Psychosomatic Problems will be held May 3 and 4, 1947 at Haddon Hall, Atlantic City. Dr. James L. Halliday, of Scotland, whose research in psychosomatic medicine is well known, will be one of the guest speakers. The following papers will be presented on Saturday, May 3:

The Role of Somatic Trigger Areas in the Mechanism of Certain Projection Phenomena of Hysteria. Dr. Janet Travell and Dr. Nolton H. Bigelow

Psychodynamics of Parkinsonism. Dr. Gotthard Booth

Preliminary Report on a Psychosomatic Study of Rheumatoid Arthritis. Dr. Adelaide Johnson

Psychosomatic Medicine and the Problem of Rheumatism. Dr. James L. Halliday

Studies of Syncope: IV. Biological Interpretation og Vasodepressor Syncope. Dr George L. Engel and Dr. John Romano

The Necessity for Reorientation in Medical Education from the Psychosomatic Point of View: The Medical Curriculum. Dr. Charles Aring; Undergraduate Training. Dr. Thomas A. C. Rennie

Psychosomatic Medicine and Problems of Society. Dr. James L. Halliday

Sound Motion Picture Presentation of a Case of Multiple Dissociation of the Personality. Dr. John G. Lynn IV and Dr. Raymond Sobel

Novel Panoramas in Psychosomatic Medicine. Dr. Bertram D. Lewin

On Sunday there will be a panel discussion, "A Survey of Several Psychodiagnostic Methods," in which Dr. Elizabeth Hellersberg, Dr. Max Hutt, Dr. Caren Machover and Dr. Bela Mittelman will participate.

Room reservations may be made directly through the hotel or the American Society for Research in Psychosomatic Problems, but dinner reservations must be made through the Society's office at 714 Madison Avenue, New York 21, New York.

American Academy of Allergy.—The American Academy of Allergy, in cooperation with the Medical Faculty of the University of California, will offer an orientation course in clinical allergy for general practitioners at the University of California Hospital, San Francisco, from July 7 to July 11 inclusive, under the auspices of Medical Extension, University of California. This course has received the approval of the Committee on Education of the American Academy of Allergy.

Book Reviews

Las neuro-bartonelosis: Sindromes neuropsiquicos de la entermedad de Carriôn—verruga peruana. By Juan B. Lastres, M.D. Price, unknown. Pp. 161. Lima, Peru: Editora medica peruana, S. A., 1945.

With the term "neurobartonellosis" the author classifies the neuropsychic syndromes of Carrion's disease which in their various forms constitute the integral part of its clinical picture. This interesting and important disease is ably and logically discussed with the help of numerous case studies compiled from the literature and from the author's experience and represents many years of observations.

A complete historical outline constitutes the initial chapter of the monograph. In sequence the scientific milestones which have led to the present day status of knowledge on the subject of Carrion's disease are reviewed. In the following chapter the author presents a thorough discussion on the pathologic anatomy of the disease. The characteristic pathologic lesions are adequately described, and an excellent series of photomicrographs is used to illustrate the micropathologic features. Following immediately is the classification and description of the various symptomatic and syndromic clinical pictures which constitute neurobartonellosis. The author's classification successfully individualizes the different neuropsychic syndromes from the maze of nervous symptoms which characterizes the disease. The next two chapters discuss in succession the effects of the disease on the vegetative nervous system, on the endocrine system and on the physicochemical, cytologic and serologic characteristics of the spinal fluid. An important discussion follows on the causation and pathologic changes of the disease, strong emphasis being laid on their relationship to the onset and course of the neuropsychic syndromes. In this section the author presents and substantiates his concept of a circumstantial affinity of the Bartonella bacilliformis for nerve elements as opposed to the theoretic existence of a neurotropic Bartonella. In the final chapters the factors involved in the diagnosis, the prognosis and the treatment of neurobartonellosis are discussed with special reference to the latest advancements made in these fields.

Dr. Lastres makes use of an extensive bibliography, which is readily obtainable from the monograph if further investigation is desired. His work is an authoritative source of reference and information and adequately covers a subject which has been largely neglected up to the present time in the study of Carrion's disease.

Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization. By J. M. Nielsen, M.D. Second edition. Price, $5. Pp. 292, with 59 illustrations. New York: Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1946.

This monograph is a significant enlargement of the author's first edition of 1936. The chief additions consist of new and greatly expanded evidence for the author's formulations. This evidence is presented in a long chapter, which constitutes almost two thirds of the book. In an appendix a proposed new nomenclature is offered, differing from the old terminology chiefly in the frequent addition of an anatomic adjective to indicate the location of the lesion in each type of disturbance. An index greatly increases the usefulness of the book for reference.

If this, the most modern American treatise on the subject, fails of complete clarity, it is not so much the fault of the author, who has devoted tireless energy to his task, as of the complexity of the material. When agnosia, apraxia and aphasia are thoroughly understood, and their psychologic, physiologic and anatomic correlations are adequately known, the clinical application will remain surpassingly arduous because of the tedious study necessary in each case. It is to the author's

great credit that his efforts have materially advanced our knowledge and that this compact book offers so thorough a treatise in so difficult a field.

Preoperative and Postoperative Treatment. Edited by Lieut. Col. Robert L. Mason and Harold A. Zintel, M.D. Second edition. Price, $7. Pp. 584, with 157 illustrations. Philadelphia: W. B. Saunders Company, 1946.

The second edition of this book follows the first edition after a period of nine years. The contributing authors are Robert H. Aldrich, G. Kenneth Coonse, Laurence B. Ellis, E. Parker Hayden, Robert M. Kark, Donald King, Robert R. Linton, Robert L. Mason, Leland S. McKittrich, Louis E. Phaneuf, George C. Prather, Lyman Richards, Dwight L. Siscoe, Judson A. Smith, Alexander W. Souter, John W. Strieder, Arthur L. Watkins, Walter R. Wegner, Sidney C. Wiggin and Harold A. Zintel.

Almost all phases of preoperative and postoperative treatment are covered. The presentation is based both on the experience of the authors and on their review of pertinent literature. In addition to the general considerations concerning preparation of the patient in whose case the risk will be slight, other factors of age and operative risk are covered. Special attention is given to various disorders, such as nutritional diseases, cardiac disease, hypertension and nephritis and diabetes. The question of anesthesia is well considered not only in the chapter bearing that title but at intervals during discussions of other subjects. Postoperative care after the uncomplicated abdominal operation is given a good deal of attention as well as the subjects of shock, water balance, blood transfusion and acidosis and alkalosis. Care of the wound is discussed and also postoperative pulmonary complications, as well as complications of the urinary tract and venous thrombosis. There are chapters on superficial burns and on physical medicine in surgical practice. All these constitute part I of the book.

In part II the preoperative and postoperative care of patients is considered with respect to operations on various anatomic divisions of the body. Chapters deal with the ear, nose and throat, hyperthyroidism, thoracic operations, gallbladder and biliary tract, stomach and duodenum, appendix, gynecologic operations, operations on the colon and rectum and urologic surgery. A final chapter on traumatic injuries includes consideration of first aid. A valuable appendix, giving laboratory findings in blood and urine in health and disease, is included. The book is well indexed and is a valuable addition to the medical library of any practicing physician.

Undersøgelser af insulinets virkning: specielt paa blodsukkeret og det respiratoriske stofskifte ved kulhydratrig og kulhydratfattig kost. By Knud Lundboek. Pp. 209. Copenhagen: Ejnar Munksgaard, 1943.

The reviewer of this book is handicapped because his lack of reading knowledge of the Danish language limits his consideration of the monograph to its accompanying English summary and to a study of the charts and graphs.

Reported are observations on the effect of larger and smaller doses of insulin on a group of psychiatric patients given insulin for inducing hypoglycemic shock. The author regards these subjects as normal from the standpoint of metabolism and therefore considers that his observations are of general significance. They cover especially the effect of insulin and the induced hypoglycemia on the respiratory quotient with the subject subsisting on diets either high in carbohydrate (512 Gm.) or relatively low in carbohydrate (135 Gm.). He concludes that insulin inhibits hepatic glycogenolysis and that a diet poor in carbohydrate diminishes this inhibition.

Also considered are the changes effected by insulin in production of heat, respiration, ventilation and the p_H of the blood.

The author regards the respiration in profound hypoglycemia as characteristic of this state of metabolism, as much so as Kussmaul's respiration is characteristic of diabetic acidosis. The respiration is marked by changing depths of respiration, irregular jerky expirations and pauses after each phase of the respiratory cycle.

Anesthesia in General Practice. By S. C. Cullen, M.D. Price, $3.50. Pp. 260, with illustrations. Chicago: The Year Book Publishers, Inc., 1946.

This finely printed and well illustrated little book covers in a thorough manner the entire subject of anesthesia—inhalation, spinal, regional, etc. The fundamental preliminaries are adequately discussed as well as complications and sequelae. The illustrations are numerous, well selected and well reproduced, but in the reviewer's mind nothing is added by the introduction of a number of childish, if harmless, cartoons to illustrate the dire effects of certain incorrect procedures.

Tumores broncogénicos. By Dr. Hernán D. Aguilar. Pp. 438. Buenos Aires, Argentina: El Ateneo, 1946.

The author's aim in writing this book was to provide a guide to physicians of the Argentine who are interested in the study of thoracic diseases and who desire to visit medical centers concerned with their treatment in the United States. With this purpose in mind, a section of the book is devoted to a review of bronchogenic tumors, clinical material acquired by Dr. Aguilar at the Barnes Hospital. The second, and last, section of the book is dedicated to observations on the general aspects of thoracic surgery in the United States, as interpreted by the author during his stay in this country.

The pathologic physiology, the diagnosis and the anatomicophysiologic basis of the surgical treatment of bronchogenic malignant growths are extensively discussed in the preliminary chapters of the first section. A clinical and surgical survey of 264 cases, with fifty-two pneumonectomies, is presented as the nucleus of this discussion of bronchogenic tumors. Also discussed are the concept of mixed pulmonary tumors and the technic of pneumonectomy, including its complications and their treatment.

In the second section the author takes up the teaching of thoracic surgery in American medical schools and hospitals. The organization of medical and surgical services for thoracic treatment in American medical centers is described, and a chapter is devoted to a description of sanatoriums for patients with tuberculosis in this country.

The book's two subjects are totally unrelated except in their common purpose. It is felt that this end is satisfactorily achieved, and the book should be of great value to the group of physicians for whom it has been written. A comprehensive bibliography is included.

Renal Diseases. By E. J. Bell, M.D. Price, $7. Pp. 434, with 119 illustrations. Philadelphia: Lea & Febiger, 1946.

Dr. Bell's work on renal disease is too well known to require much comment. In this finely printed book, with many figures of gross and microscopic pathologic material, Bell gives a systematic discussion of renal diseases of all sorts. While the whole subject is covered, Dr. Bell's own extensive experience lends special weight to certain sections; his intimate knowledge of the pathology of renal disease is also impressive. Comprehensive bibliographies will be found especially useful by the critical reader.